Pergamon

Tetrahedron Letters, Vol. 35, No. 49, pp. 9293-9296, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02044-2

A One-pot Synthesis of Nitrohydroxylated Pyrrolidine and Piperidine Ring Systems by Tandem Michael-Henry Reaction.

Achille Barco[a], Simonetta Benetti[a], Carmela De Risi[b], Gian P. Pollini[b], Romeo Romagnoli[a] and Vinicio Zanirato[b].

[a] Dipartimento di Chimica - Via L. Borsari 46, I-44100 Ferrara

[b] Dipartimento di Scienze Farmaceutiche - Via Fossato di Mortara 19, I-44100 Ferrara

Abstract: Nitrohydroxylated pyrrolidine and piperidine ring systems are conveniently obtained through a one-pot procedure involving sequential Michael-Henry reaction between nitroethylene and a nitrogen nucleophile incorporating a suitably placed precursor for the generation either reductively or oxidatively of an aldehyde group which is directly trapped in the subsequent nitroaldolization step.

Interest in biologically and synthetically important polyhydroxylated pyrrolidine and piperidine ring systems with well defined stereochemistry has often evolved in the development of new methodologies for their synthesis.[1-5]

Tandem reaction based methodologies for the synthesis of biologically active compounds have witnessed a striking progress over the last years[6] and have been recently reviewed.[7]

In connection with our program dealing with the tandem annulation chemistry of unsaturated nitroderivatives,[8-10] we wish to report in this paper an efficient one-pot procedure for the construction of nitrohydroxylated pyrrolidine and piperidine derivatives.

As summarized in the Scheme 1, our own strategy entails on easy intramolecular nitroaldol reaction (Henry reaction) of nitroalkane adducts deriving by intermolecular Michael addition between nitroethylene and a nitrogen nucleophiles, bearing at the α- or β-position suitable functionalities from which an aldehyde function could be generated either by oxidative or reductive processes.

To test the feasibility of our protocol we prepared several simple fragments containing both the nitrogen nucleophile and the required aldehyde precursor in a different oxidation state in a straightforward manner

starting from commonly available chemicals such as benzylamine, benzaldehyde, ethanolamine, methyl glyoxylate and methyl acrylate.[11]

Thus, the bifunctional fragment **1a** required for the construction of pyrrolidine derivatives was easily prepared by standard chemistry, involving *N*-benzylation of ethanolamine through hydrogenation in the presence of 5% Pd/C of the corresponding imine with benzaldehyde, while the Michael adduct **2b** between benzylamine and methyl acrylate and the corresponding primary alcohol **1b** was simply derived by subsequent $LiAlH_4$ reduction. Both represent suitable homologous units for piperidine ring construction.

Treatment of crude *N*-benzylated ethanolamine **1a** or the homologous **1b** with 2-benzoyloxy-1-nitroethane, utilized as stable precursor for nitroethylene,[12] proceeded uneventfully to give the expected Michael adducts, which were directly submitted to Swern oxidation[13] allowing the corresponding hydroxylated nitropyrrolidine **3a** or piperidine **3b** to be isolated in 38 and 44% overall yield respectively[14] after column chromatography on silica gel. (Scheme 1).

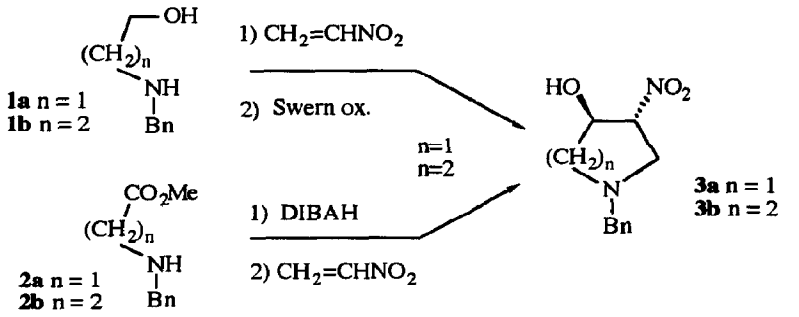
On the other hand, DIBAH reduction[15] at -78°C of the aminoester derivatives **2a** and **2b**, followed sequentially by quenching with methanol and addition of 2-benzoyloxy-1-nitroethane allowed the same compounds to be obtained in 45 and 67% overall yield.

In summary, we have developed a protocol that allows hydroxylated pyrrolidine and piperidine derivatives containing an additional nitro group to be obtained conveniently, the extremely rich chemistry of which may allow a variety of useful functional group interconversion or removal.

Thus, these compounds could be easily reduced to the corresponding amines in quantitative yield by hydrogenation in the presence of Raney nickel (W4), while removal of the nitro group could be efficiently accomplished on treatment with TBTH in the presence of a catalytic amount of AIBN.[16]

Moreover, this experimentally simple one-pot procedure based on the use of easily accessible starting material, presents the additional advantage of generating "*in situ*" the often unstable and capricious aminoaldehydes.

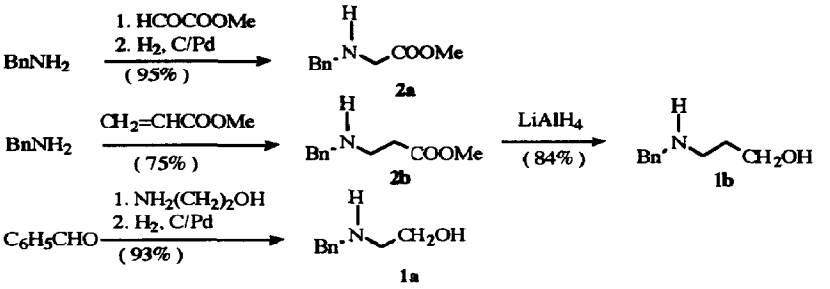
Scheme 1



Acknowledgement: We gratefully acknowledge the "Progetto Finalizzato Chimica Fine e Secondaria II" and Murst (60%) for generous financial support.

References and Notes.

1. Ikota, N.; Hanaki, A., *Heterocycles*, **1988**, *11*, 2535-2537.
2. Sinnot, M.L., *Chem. Rev.*, **1990**, *90*, 1171-1202.
3. Fleet, G.W.J.; Witty, D.R., *Tetrahedron Asymmetry*, **1990**, *1*, 119-136.
4. Griffart-Brunet, D.; Langlois, N., *Tetrahedron Lett.*, **1994**, *35*, 2889-2890.
5. Griffart-Brunet, D.; Langlois, N., *Tetrahedron Lett.*, **1994**, *35*, 119-122.
6. Posner, G.H.; Crouch, R.H., *Tetrahedron*, **1990**, *46*, 7509-7530.
7. Tietze, L.F.; Beifuss, U., *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 131-163.
8. Barco, A.; Benetti, S.; Casolari, A.; Pollini, G.P.; Spalluto, G., *Tetrahedron Lett.*, **1990**, *31*, 3039-3042.
9. Barco, A.; Benetti, S.; Casolari, A.; Pollini, G.P.; Spalluto, G.; Zanirato, V., *J. Org. Chem.*, **1992**, 6279-6286.
10. Barco, A.; Benetti, S.; De Risi, C.; Pollini, G.P.; Spalluto, G.; Romagnoli, R.; Zanirato, V., *Tetrahedron*, **1994**, *50*, 2583-2590.
11. The preparation of the required bifunctional units is outlined below. The reported yields refer to crude isolated products.



12. Barco, A.; Benetti, S.; Pollini, G.P.; Spalluto, G., *Synthesis*, **1991**, 479-480.
13. Ireland, R.E.; Norbeck, D.W., *J. Org. Chem.*, **1985**, *50*, 2198-2200.
Typical procedure: To a cooled (-78°C) and stirred solution of oxalyl chloride (4.48 mmol, 0.4 ml) in dry THF (20 ml) was added DMSO (8.27 mmol, 0.64 ml) via syringe at such a rate that the temperature was maintained below -60°C. After stirring for 15 min, a solution of the nitroalcohol (840 mg, 3.75 mmol) in THF (10 ml) was slowly added while the temperature was maintained below -60°C. Stirring was continued for an additional 20 min, then Et_3N (28.7 mmol, 4 ml) was added and the resulting mixture was allowed to warm to room temperature over 1h. Quenching was achieved by addition of a saturated solution of $NaHCO_3$ (5 ml). The reaction mixture was extracted with ether (2 x 20ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated and the residue purified by flash chromatography (eluent: ether-light petroleum 2:1) to afford **3a** (320 mg, 38%) as a yellow oil.
14. All compounds have been fully characterized by analytical and spectroscopic methods. The structures of **3a** and **3b** were assigned on the basis of their ^1H NMR spectral data (COSY, NOE, decoupling).
3a : oil; IR (neat): 3200-3500, 1550, 1360, 1050-1150 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ: 2.55-2.65 (dd, 1H, J = 4.4, 10.6 Hz, CH*H* CHOH), 2.65-2.7 (bs, 1H, O*H*), 3-3.1 (dd, 1H, J = 5 and 10.3 Hz, C*H* HCHOH), 3.1-3.2 (m, 2H, C*H* $_2$CHNO$_2$), 3.66-3.70 (s, 2H, C*H* $_2$Ph), 4.7-4.9 (m, 2H, C*H* OH and C*H* NO$_2$), 7.3-7.5 (m, 5H, Ph).

^{1}H NMR (CD_3OD): δ 2.4-2.5 (dd, 1H, J = 6Hz, 10.8 Hz, CH*H* CHOH), 2.94-2.99 (AB system, 1H, J=10.9 Hz, CH*H* CNO$_2$), 3.05-3.15 (dd, 1H, J = 5, 10.3 Hz, C*H* HCHOH), 3.2-3.26 (AB system, 1H, J = 11.1 Hz, C*H* HCNO$_2$), 3.54-3.74 (AB system, 2H, J = 12.8 Hz, C*H* $_2$Ph), 4.6-4.7 (t, 1H, J = 5 Hz, C*H* OH), 7.3-7.5 (m, 5H, Ph).

3b : oil; IR (neat) : 3400, 1540, 1350, 1050, 730 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 0.8-0.9 (m, 1H, NCH$_2$CH*H* CHO), 1.6-1.9 (dq, 1H, J = 2.8, 9, 12, 24 Hz, NCH$_2$C*H* HCHOH), 2-2.1 (m, 1H, NC*H* HCH$_2$CHOH), 2.1-2.2 (dq, 1H, J = 2.8, 12, 24 Hz, NCH*H* CH$_2$CHOH), 2.5-2.6 (m, 1H, O*H*), 2.8-3 (ddd, 1H, J = 1.6, 9, 12 Hz, C*H* HCHNO$_2$), 3.3-3.4 (ddd, 1H, J = 1.8, 4.5, 12 Hz, C*H* HCHNO$_2$), 3.6 (m, 2H, C*H* $_2$Ph), 4.1-4.2 (m, 1H, C*H* OH), 4.4-4.6 (m, 1H, C*H* NO2 ,7.3 (m, 5H, Ph).

15. Typical procedure: a solution of diisobutylaluminium hydride (1M in hexane, 32.6 ml) was added dropwise to a stirred and cooled (-78°C) solution of **2b** (2.1g, 10.87 mmol) in toluene (30ml). After stirring for 1h at -78°C, methanol (10ml) was added dropwise, the cold bath was removed and then a solution of 2-benzoyloxy 1-nitroethane (2.1g, 10.87 mmol) in methanol (5ml) was added and the reaction mixture was left for 1 h to warm at 25°C. The inorganic solids were filtered through Celite and washed with MeOH (20ml). The organic phase was concentrated and the residue dissolved in ether (15ml), washed with a saturated solution of $NaHCO_3$ (5 ml), dried, evaporated and the residue purified by flash chromatography (ether : light petroleum 2:1) to give **3b** (1.7g, 67%) as a yellow oil.

16. Ono, N.; Miyake, H.; Kaji, A., *J. Org. Chem.*, **1984**, *49*, 4997-4999.

(*Received in UK* 8 *September* 1994; *revised* 11 *October* 1994; *accepted* 14 *October* 1994)