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Tetrahedron Letters 45 (2004) 1373–1375
Tetrahedron Letters

A new 'one-pot' synthesis of 2-substituted 3-nitropyrrolidines through a multicomponent domino reaction

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Received 5 November 2003; revised 24 November 2003; accepted 11 December 2003

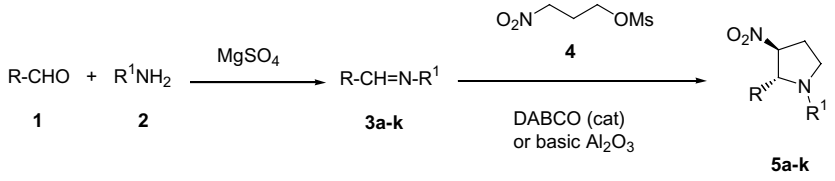
Abstract—An efficient 'one-pot' synthesis of the title compounds based on a multicomponent domino reaction between imines and 3-nitro-1-propanol methanesulfonate has been developed.

Pyrrolidines are ubiquitous structural units in many naturally occurring alkaloids with biological activity, such as hygrine, nicotine, tropine or cocaine, and in drug and drug candidates displaying a wide variety of activities.[1] Other compounds having this moiety include amino acids such as proline or kainic acid. Furthermore, these heterocyclic rings are of interest in synthetic organic chemistry as chiral auxiliaries[2] as well as for their unique ability to induce well-defined molecular architecture in peptidomimetic compounds.[3] As a result, much effort has been expended on the development of stereocontrolled syntheses of substituted pyrrolidines.[4,5]

Recently multicomponent reactions have attracted a great deal of interest due to the possibility of generating molecular diversity in a minimum number of steps. As a part of our continuous interest directed towards the development of new methodologies for the synthesis of five- and six-membered nitrogen heterocycles, we report in preliminary form the results of our recent efforts devoted to the synthesis of functionalized pyrrolidines.

The new methodology allowed us to prepare 2-substituted 3-nitro-pyrrolidines **5a**–**k** (Scheme 1) through a one-pot process, which can be defined both as an aza-Henry[6] and a nitro-Mannich reaction[7] between imines **3a**–**k** and 3-nitro-1-propanol methanesulfonate **4**. This hitherto unknown compound[8] was efficiently prepared by esterification with triethylamine/methanesulfonyl chloride of the readily available 3-nitro-1-propanol, in turn conveniently prepared by sodium borohydride reduction of the corresponding aldehyde.[9]

We anticipated that this bifunctional reagent could take part in a domino sequence initiated by addition to the carbon–nitrogen double bond of an imine derivative by virtue of the well-known properties of the nitro group followed by subsequent intramolecular substitution of



Scheme 1.

Keywords: Multicomponent domino reactions; Aza-Henry reactions; Nitro-Mannich reactions; Pyrrolidines.
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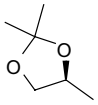
doi:10.1016/j.tetlet.2003.12.071

Table 1

Entry	Aldehydes R	Amines R^1	Aldimines	Pyrrolidines[a] (% yield)	General procedure
1	CH_3	Bn	**3a**	**5a** (63)	A
2	C_2H_5	Bn	**3b**	**5b** (65)	A
3	C_3H_7	Bn	**3c**	**5c** (65)	A
4	*n*-C_6H_{13}	Bn	**3d**	**5d** (90)	A
5	*n*-C_9H_{19}	Bn	**3e**	**5e** (89)	A
6	C_6H_5	Bn	**3f**	**5f** (70)	A
7	3-Pyridyl	Bn	**3g**	**5g** (55)	B
8	3-Pyridyl	C_6H_5	**3h**	**5h** (67)	B
9	C_6H_5	C_6H_5	**3i**	**5i** (70)	B
10	*n*-C_7H_{15}	$C_6H_5CH(CH_3)$	**3j**	**5j** (69)[b,e]	B
11		Bn	**3k**	**5k** (52)[c,e] (67)[d,e]	A B

[a] Isolated yields after flash chromatography.
[b] 9:1 mixture of diastereomers.
[c] 3:1 mixture of diastereomers.
[d] 4:1 mixture of diastereomers.
[e] Dr values were measured by HPLC.

the mesyl moiety by nucleophilic attack of the β-nitroamine generated during the first addition.

Initial attempts to carry out the reaction simply by mixing equimolar amounts of the three components, namely aldehyde, amine and 3-nitro-1-propanol methanesulfonate in dichloromethane at room temperature produced very low yields of the expected product (5–15%). However, we were able to optimize the reaction conditions by separately forming the aldimine component (prepared by treating equimoleculars amounts of aldehyde and amine in the presence of anhydrous magnesium sulfate) followed by reaction with 1 equiv of 3-nitro-1-propanol methanesulfonate in the presence of a catalytic amount of DABCO or basic aluminium oxide.[10]

In this way, the expected pyrrolidines **5a**–**k** were formed in satisfactory yields (52–90%) in most cases as a single diastereomer, namely that possessing the *trans*-stereochemistry between the nitro group at position 3 and the substituent at position 2, the *cis*-isomer being in some cases present in trace amounts.[11] The structures of compounds **5a**–**k** could be unambiguously assigned by ^{1}H NMR analysis on the basis of the low value of the coupling constant between H-2 and H-3 ($J = 0$–2.5 Hz), which is consistent with a $\sim 90°$ dihedral angle.

Moreover, we have also tried to induce asymmetry in our protocol using chiral amine or aldehyde components. To this end, we investigated the reaction of the imine component **3j** derived from (*S*)-(−)-phenylethylamine and 1-heptanal with 3-nitro-1-propanol methanesulfonate, which afforded the expected pyrrolidine **5j** with good asymmetric induction (de 80% by HPLC).

Analogously, the reaction of the aldimine **3k** derived from D-glyceraldehyde-isopropylidene acetal and benzylamine with 3-nitro-1-propanol methanesulfonate produced the expected pyrrolidines **5k** in good yield and satisfactory diastereoisomeric excess. Our results are summarized in Table 1.

These preliminary results demonstrate that the methodology reported here represents a new short and efficient route to the preparation of 2,3-disubstituted pyrrolidines starting from very simple materials, such as aldehydes and 3-nitro-1-propanol methanesulfonate.

This strategy is widely applicable to the synthesis of both simple and complex structures enabling the preparation of additional compounds owing to the versatility of the nitro group.[12] As an example, the pyrrolidine **5g** could be easily converted to a nicotine precursor[13] by tributyltin hydride-promoted radical substitution of the nitro group by hydrogen.

In conclusion, we have identified suitable conditions employing an experimentally simple pathway for the synthesis of 2-substituted 3-nitro-pyrrolidines, which are useful building blocks in organic synthesis. We are now actively studying a new catalytic version of this strategy inspired by the recent attention dedicated to the asymmetric version[14] of the nitro-Mannich reaction as a tool for the synthesis of 1,2-diamines.

Acknowledgements

We wish to thank the Ministry of University (MIUR) for financial support (PRIN 2002).

References and notes

1. O'Hagan, D. *Nat. Prod. Rev.* **2000**, *17*, 435–446, and previous annual reports in this series.
2. Wang, Q.; Sasaki, N. A.; Riche, C.; Potier, P. *J. Org. Chem.* **1999**, *64*, 8602–8607, and references cited therein.

3. Millet, R.; Domarkas, J.; Rombaux, P.; Rigo, B.; Houssin, R.; Henichart, J.-P. *Tetrahedron Lett.* **2002**, *34*, 5087–5088.
4. Pichon, M.; Figadère, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964.
5. Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 477–501.
6. Westerman, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151–153.
7. Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932–9934.
8. Preparation of 3-nitro-1-propanol methanesulfonate **4**: To a cooled (0 °C) solution of 3-nitro-1-propanol[9] (2 g, 1.9 mmol) in dichloromethane (4 mL), methanesulfonyl chloride (2.18 g, 1.9 mmol) and triethylamine (1.92 g, 1.9 mmol) were added. After stirring at 0 °C for 15 min the reaction mixture was washed with brine, dried (anhydrous Na_2SO_4) and the solvent evaporated under reduced pressure. The crude oil was dissolved in dichloromethane and rapidly passed through a short column of Florisil® (Fluka, 60–100 mesh).
   IR (film): 1540, 1360, 1340, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.21 (quintet, 2H, $J = 7$ Hz, CH_2), 3.05 (s, 3H, CH_3OSO_3), 4.18 (t, 2H, $J = 7$ Hz, CH_2OMs), 4.56 (t, 2H, $J = 7$ Hz, CH_2NO_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.8, 37.4, 65.6, 71.2.
9. (a) Öhrlein, R.; Schwab, W.; Ehrler, R.; Jäger, V. *Synthesis* **1986**, 535–538; (b) Griesser, H.; Öhrlein, R.; Schwab, W.; Ehrler, R.; Jäger, V. *Org. Synth.* **1999**, *77*, 236.
10. General procedure A: A mixture of aldehyde (0.1 mmol), amine (0.1 mmol) and anhydrous $MgSO_4$ (1.5 g) in CH_2Cl_2 (4 mL) was stirred at room temperature for 12 h. The solid was removed by filtration and the solvent was reduced to half of its original volume in vacuo. Nitro derivative **4** (0.1 mmol) and a catalytic amount of DABCO were added and the reaction mixture was stirred overnight. After removal of the solvent under reduced pressure the residual oil was purified by flash chromatography (ethyl acetate/cyclohexane).
    General procedure B: The nitro derivative **4** (1 mmol) and basic aluminium oxide (1 g) were added to a solution of the imine (1 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was left at room temperature overnight, then diluted with ethyl acetate, filtered and the solvent removed under reduced pressure. The residual oil was purified by flash chromatography (ethyl acetate/cyclohexane).
11. Selected data for compounds **5a–k**. **5a**: oil; IR (film): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39 (3H, d, $J = 6.2$ Hz), 2.19–2.32 (1H, m), 2.35–2.42 (1H, m), 2.45–2.60 (m, 1H), 2.93–3.20 (m, 2H), 3.25 (1H, d, $J = 13.0$ Hz), 4.10 (1H, d, $J = 13.0$ Hz), 4.61 (1H, ddd, $J = 9.5$, 6.0, 2.5 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.9, 28.5, 52.1, 57.3, 65.3, 91.2, 127.2, 128.7, 128.8, 138.3. **5b**: oil; IR (film): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.99 (3H, t, $J = 7.0$ Hz), 2.60 (2H, quintet, $J = 7.0$ Hz), 2.38 (4H, m), 2.99 (1H, dt, $J = 7.0$, 2.5 Hz), 3.37 (1H, d, $J = 13.0$ Hz), 4.00 (1H, d, $J = 13.0$ Hz), 4.73 (1H, ddd, $J = 7.6$, 5.0, 2.5 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3, 14.0, 21.3, 29.3, 51.5, 57.1, 88.1, 127.2, 128.3, 128.6, 138.8. **5c**: oil; IR (film): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.90 (3H, t, $J = 6.4$ Hz), 1.25–1.80 (4H, m), 2.10–2.23 (1H, m), 2.25–2.36 (1H, m), 2.45–2.61 (1H, m), 2.90–2.98 (1H, m), 3.01–3.08 (1H, m), 3.37 (1H, d, $J = 13.0$ Hz), 4.00 (1H, d, $J = 13.0$ Hz), 4.75 (1H, m), 7.20–7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 18.3, 30.0, 34.8, 52.2, 58.0, 69.5, 89.8, 127.1, 128.3, 128.6, 138.8. **5d**: oil; IR (film): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.89 (3H, t, $J = 6.6$ Hz), 1.20–1.88 (10H, m), 2.40–2.70 (2H, m), 2.52 (1H, ddd, $J = 10.2$, 6.4, 6.6 Hz), 2.98 (1H, dt, $J = 8.0$, 2.4 Hz), 3.05 (1H, ddd, $J = 10.2$, 7.8, 3.8 Hz), 3.38 (1H, d, $J = 13.0$ Hz), 4.00 (1H, d, $J = 13.0$ Hz), 4.73 (1H, ddd, $J = 8.2$, 4.6, 2.4 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 22.4, 25.1, 29.6, 30.2, 32.0, 32.8, 52.5, 58.3, 69.9, 90.0, 127.4, 128.6, 128.9, 138.3. **5e**: oil; IR (film): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.89 (3H, t, $J = 6.4$ Hz), 1.19–1.82 (16H, m), 2.05–2.40 (2H, m), 2.50–2.31 (1H, m), 2.94 (1H, dt, $J = 8.8$, 2.2 Hz), 2.95–3.10 (1H, m), 3.35 (1H, d, $J = 14$ Hz), 4.00 (1H, d, $J = 14.0$ Hz), 4.73 (1H, ddd, $J = 7.4$, 4.2, 2.2 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 22.6, 25.0, 29.4, 30.0, 30.1, 30.2, 30.3, 31.8, 32.6, 52.4, 58.2, 69.7, 89.5, 127.2, 128.4, 128.8, 138.8. **5f**: mp 45.5 °C; IR (nujol): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.39–2.45 (2H, m), 2.60–2.75 (1H, m), 3.15–3.20 (1H, m), 3.21 (1H, d, $J = 12.8$ Hz), 3.85 (1H, d, $J = 12.8$ Hz), 3.95 (1H, d, $J = 2.5$ Hz), 4.82 (1H, ddd, $J = 9.5$, 6, 2.5 Hz), 7.21–7.55 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.6, 51.6, 57.3, 74.1, 92.3, 127.3, 127.7, 128.4, 128.7, 129.0, 129.1, 138.3, 139.2. **5g**: oil; IR (film): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.35–2.55 (2H, m), 2.60–2.70 (1H, m), 3.20–3.41 (1H, m), 3.45 (1H, d, $J = 12.8$ Hz), 3.78 (1H, d, $J = 12.8$ Hz), 4.00 (1H, d, $J = 6.0$ Hz), 4.68–4.78 (1H, m), 7.19–7.35 (5H, m), 7.43 (1H, dd, $J = 7.8$, 5.2 Hz), 7.90 (1H, dt, $J = 7.8$, 1.8 Hz), 8.70 (1H, dd, $J = 5.2$, 1.8 Hz), 8.80 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.7, 31.7, 37.3, 71.3, 91.7, 124.3, 127.3, 128.4, 128.6, 135.7, 136.3, 137.5, 149.2, 149.7. **5h**: mp 119 °C (1:1 ether/petroleum ether); IR (nujol): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.41–2.59 (1H, m), 2.79–2.91 (1H, m), 3.65–3.81 (1H, m), 3.85–3.98 (1H, m), 4.90 (1H, d, $J = 6.0$ Hz), 5.40 (1H, s), 6.50 (2H, d, $J = 7.8$ Hz), 6.76 (1H, t, $J = 7.8$ Hz), 7.16 (2H, d, $J = 7$ Hz), 7.24 (1H, m), 7.64 (1H, m), 8.60 (1H, m), 8.75 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.9, 46.9, 69.7, 85.7, 113.2, 119.3, 127.7, 128.9, 136.9, 138.1, 144.7, 149.8, 156.8. **5i**: mp 92.5 °C (1:1 ether/petroleum ether); IR (nujol): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.35–2.59 (1H, m), 2.72 (1H, ddd, $J = 1.6$, 4.0, 14.4 Hz), 3.65–3.85 (1H, m), 3.87 (1H, dt, $J = 13.0$, 1.4 Hz), 4.91 (1H, d, $J = 6.0$ Hz), 5.20 (1H, s), 6.50 (2H, d, $J = 7.6$ Hz), 6.73 (1H, t, $J = 7.6$ Hz), 7.18 (2H, d, $J = 7.6$ Hz), 7.22–7.55 (5H, m). **5j**: major diastereomer: oil, $[\alpha]_D^{25}$ −1.81° (*c* 0.83, $CHCl_3$); IR (film): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.85 (3H, t, $J = 6.6$ Hz), 1.38 (3H, d, $J = 6.2$ Hz), 1.20–1.88 (10H, m), 2.05–2.22 (2H, m), 2.35–2.42 (1H, m), 2.80–2.98 (2H, m), 3.30–3.40 (1H, m), 3.80 (1H, q, $J = 6.2$ Hz), 4.65 (1H, ddd, $J = 7.4$, 4.2, 2.0 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 17.9, 22.5, 25.4, 26.9, 28.4, 31.7, 32.8, 47.9, 59.9, 67.1, 89.7, 127.2, 127.6, 128.3, 137.9. **5k**: major diastereomer: oil, $[\alpha]_D^{25}$ −4.29° (*c* 0.21, $CHCl_3$); IR (film): 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (3H, s), 1.41 (3H, s), 2.15–2.40 (2H, m), 2.70–2.85 (1H, m), 2.97–3.17 (1H, m), 3.40–3.49 (1H, m), 3.73 (1H, d, $J = 13.0$ Hz), 3.75–3.82 (1H, m), 3.97–4.05 (3H, m), 4.97 (1H, ddd, $J = 7.4$, 2.4, 1.2 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.0, 26.5, 30.9, 52.8, 60.0, 66.7, 70.5, 75.1, 87.4, 109.6, 127.5, 128.5, 128.8, 138.6.
12. Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2586–2597.
13. Baxendale, I. R.; Brusotti, G.; Matsuoka, M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 143–154.
14. Tsuritani, N.; Yamada, K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276–277, and references cited therein.