Tetrahedron Letters 52 (2011) 1583–1586

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A flow chemistry route to 2-phenyl-3-(1*H*-pyrrol-2-yl)propan-1-amines

Mark Tarleton, Adam McCluskey *

Chemistry, School of Environmental and Life Sciences, University of Newcastle, Callaghan, NSW 2308, Australia

ARTICLE INFO

Article history:
Received 7 October 2010
Revised 22 December 2010
Accepted 21 January 2011
Available online 27 January 2011

Keywords:
Knoevenagel condensation
Flow hydrogenation
Selective hydrogenation
Medicinal chemistry

ABSTRACT

The Knoevenagel condensation of pyrrole-2-carboxaldehyde (**1**) with a range of substituted benzyl nitriles (**2a–e**) afforded rapid access to a family of α,β-unsaturated nitriles (**3a–e**) in good yields (67–78%). Flow hydrogenation (ThalesNano H-cube™) at 60 °C, 50 bar H_2 pressure, 1.0 mL/min through a 10% Pd-C catalyst selectively, and quantitatively, hydrogenated the olefin double bond (**4a–e**). Use of a Raney Nickel catalyst at 70 °C, 70 bar H_2 pressure and flow rates of 0.5–1.0 mL/min afforded quantitative conversion into the corresponding saturated amines with the reduction of both the olefin and nitrile bonds (**5a–e**). The versatility of this approach was further exemplified by reaction of **5a** and **5c** with norcantharidin to afford acid amide norcantharidin analogues **7** and **8** as novel protein phosphatase 1 and 2A inhibitors.

The current focus of our medicinal chemistry team is in the development of protein phosphatase 1 and 2A and dynamin GTPase inhibitors.[1–3] While targets change, all medicinal chemistry programmes require access to novel building blocks to explore new chemical space.[4] These new building blocks are initially only required in milligram quantities. As the drug development programme progresses, increased quantities of the drug are required. Thus there is a pressing need to develop elegant approaches amenable to the rapid production of novel building blocks, but also production scale-up to meet the demands of whole cell, and ultimately whole animal studies. In our case, this has demanded the development of approaches capable of delivering building blocks for libraries of **12–24** compounds and subsequent scale-up from 10 mg to 10 g.

Until recently, synthetic re-scaling required laborious re-optimisation of methods developed to access the small quantities of reagents required at the initial library synthesis stage. However, the introduction of flow chemistry has had a significant impact on our ability to deliver the required compound quantities both at the initial building block stage and the animal testing stages of our programmes.[5–9] Recently, we had cause to require rapid access to a range of novel amines of the type shown in Figure 1.[10,11]

We rationalised that access to the required amines should be attainable by a two-step process commencing from pyrrole-2-carboxaldehyde (**1**) and a range of substituted benzyl nitriles **2a–e** via a Knoevenagel condensation.[10–19] Reduction would then afford the desired analogues. In our subsequent synthetic efforts we also imposed additional constraints requiring flexible approaches that allow generation of mg to gram quantities of each of the library components. In the initial Knoevenagel approaches this was a relatively trivial proposition, and one that has been addressed by us, and others elsewhere.[10–19] However, the hydrogenation requirement stalls rapid library development in a standard laboratory environment, typically limiting this step to a batch-wise approach with the quantity of each batch limited by the available volume of the hydrogenating equipment. This is clearly a disadvantage not only in regards to high throughput, but with reaction scale-up. In efforts to accelerate both analogue development and reaction scale-up, our team has invested heavily in flow chemistry technology. Having access to the ThalesNano H-cube™ (H-cube) flow hydrogenator we turned our attention to the synthesis of Type A (**4a–e**) and Type B (**5a–e**) analogues as shown in Scheme 1.

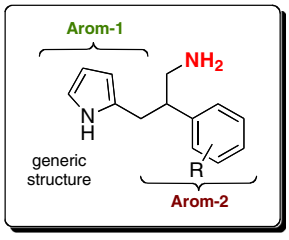


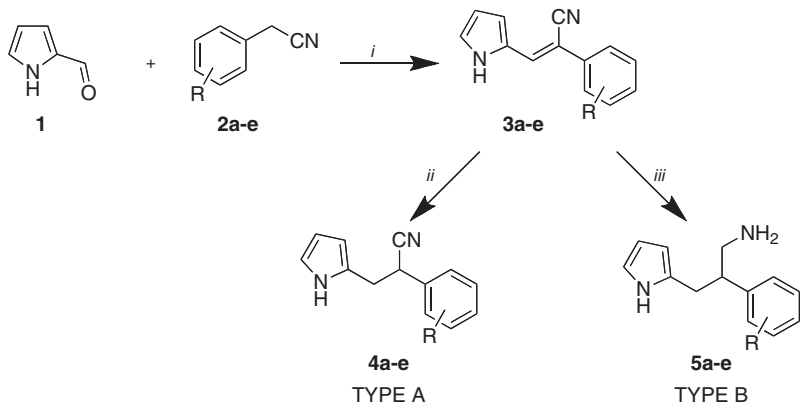
Figure 1. Generic structure of the target bis-aromatic amines.

In a typical experiment, the benzyltrimethylammonium hydroxide [$PhCH_2NMe_3(OH)$] mediated Knoevenagel condensation allowed direct access to the desired α,β-unsaturated nitriles (Scheme 1) in good yields (67–78%).[10,11,20]

With these nitriles in hand we next turned our attention to the flow hydrogenation using the H-cube. Flow chemistry approaches

* Corresponding author. Tel.: +61 2 4921 6486; fax: +61 2 4921 5472.
E-mail address: Adam.McCluskey@newcastle.edu.au (A. McCluskey).

0040-4039/$ - see front matter Crown Copyright © 2011 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.01.096



Scheme 1. Reagents and conditions: (i) H_2O, $PhCH_2NMe_3(OH)$, 50 °C, 5 h; (ii) 0.05 M **3a–e** (acetone), 10% Pd-C, 50 °C, 50 bar H_2, 1.0 mL/min, H-cube; (iii) 0.05 M **3a–e** (1 M NH_3 in MeOH), Raney Ni, 70 °C, 70 bar H_2, 0.5 mL/min, H-cube.

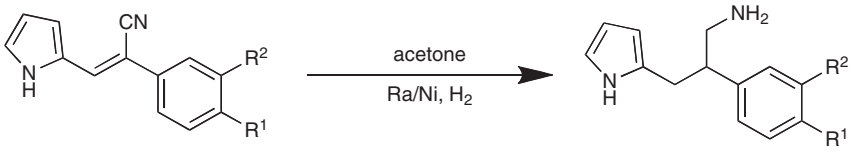
Table 1
Optimisation of temperature and H_2 pressure, for the reduction of **3a** to **5a** using a Raney Ni hydrogenation catalyst at a 1.0 mL/min flow rate. Reactions were conducted for 10 min

Entry	*P* (bar)	*T* (°C)	Conversion (%)
1	90	100	30
2	80	100	30
3	70	100	30
4	60	100	30
5	50	100	25
6	40	100	25
7	100	90	25
8	100	80	15
9	100	70	12
10	100	60	5
11	100	50	0
12	100	40	0

have facilitated rapid modification, and reaction optimisation. As only sufficient sample was required for analysis, for example, by HPLC or MS, incredibly short reaction times were feasible allowing multiple runs in a single day.[21] This greatly enhanced our ability to survey a range of reaction conditions from temperature, catalyst residence time (flow rate), stoichiometry and in this instance, hydrogen pressure. The H-cube uses pre-packed catalyst cartridges and in situ hydrogen generation from deionised water alleviating safety concerns normally associated with hydrogen gas and handling of catalyst materials.[22]

Our first series of optimisation reactions involved passing 0.05 M solutions of (*Z*)-2-phenyl-3-(1*H*-pyrrol-2-yl)acrylonitrile (**3a**) (in acetone) through each of three hydrogenation catalyst cartridges: 5% Pd-C; 10% Pd-C and Raney Nickel (Ra/Ni).[22] To best maximise the potential reduction in each instance our initial examinations were conducted at 100 °C and 100 bar H_2 pressure (H-cube 'controlled mode'), flow rate was 1.0 mL/min. No reaction was observed with the 5% Pd-C catalyst under these conditions, but complete reduction of the olefinic double bond was accomplished with the 10% Pd-C catalyst (100%),[23] and reduction of both the olefin and the nitrile moieties was accomplished with the Raney Nickel (Ra/Ni) catalyst (95%). The reduced isolated yield (95% vs 100%) with the Ra/Ni catalyst was attributed to issues with product stability and work-up. With both the catalysts we noted 100% consumption of the starting material, but with the Ra/Ni catalyst, the product was contaminated with ca. 5% of an unidentified highly polar by-product. Filtration through a silica gel plug removed this material, but afforded a slightly reduced isolated yield. The amine produced via the Ra/Ni-catalysed reduction also rapidly discoloured on exposure to air. In this latter case the amino analogue was only obtained after the feeder solution was allowed to re-circulate until no starting material was detected by mass spectrometry. While we did not explore the flow hydrogenation of the olefinic double bond in great detail, all the evaluated analogues

Table 2
Flow hydrogenation of acrylonitrile analogues **3a–e** at 60 °C and 50 bar H_2 pressure at 1.0 mL/min

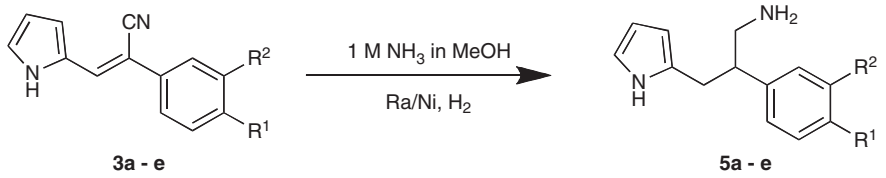


3a - e **5a - e**

Entry	R^1	R^2	Pressure (bar)	Product	Isolated yield (%)
1	H	H	50	**5a**	100
2	H	H	100	**5a**	100
3	$NO_2(NH_2)$[a]	H	50	**5b**	23
4	F	H	50	**5c**	66
5	Cl	H	50	**5d**	32
6	Cl	Cl	50	**5e**	30

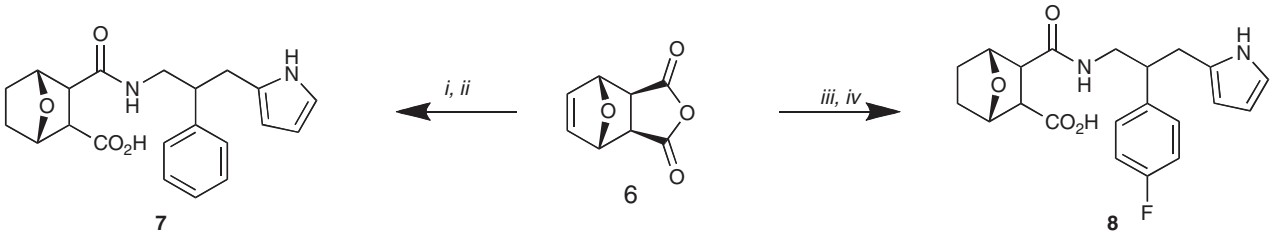
[a] The NO_2 was reduced to NH_2.

Table 3
Isolated yield of amines **5a–e** obtained by the flow reduction of **3a–e** using a Raney Ni hydrogenation catalyst at 70 °C and 70 bar H_2 pressure



Entry	R^1	R^2	Flow rate (mL/min)	Product	Yield (%)
1	H	H	0.5	**5a**	100
2	$NO_2(NH_2)$[a]	H	1.0	**5b**	100
3	F	H	0.5	**5c**	100
4	Cl	H	0.5	**5d**	100
5	Cl	Cl	0.5	**5e**	100

[a] The NO_2 was reduced to NH_2.



PP2A inhibition = 18.5 ± 3.50 μM
PP1 inhibition = 14.1 ± 7.90 μM

PP2A inhibition = 7.25 ± 1.25 μM
PP1 inhibition = 4.5 ± 1.55 μM

Scheme 2. Reagents and conditions: (i) 0.05 M solution of **6** (acetone), 50 °C, 50 bar H_2, 1.0 mL/min (H-cube); (ii) 0.05 M solution of **5a** (1 M NH_3 in MeOH); (iii) 0.05 M solution of **6** (acetone), 50 °C, 50 bar H_2, 1.0 mL/min (H-cube); (iv) 0.055 M solution of **5c** (1 M NH_3 in MeOH), 50 °C, 50 bar H_2, 1.0 mL/min (H-cube). Protein phosphatase activity (IC_{50} values) of **7** and **8**.

were smoothly and cleanly converted into the saturated nitrile analogues, **4a–e**.

Having established that the 10% Pd-C and Ra/Ni catalysts afforded two different products, and that we were unable to determine reaction conditions under which only the nitrile group was reduced (data not shown), we sought to optimise the flow hydrogenation conditions that would most expediently allow the synthesis of the desired bis-aromatic amines (see Fig. 1). In this evaluation process we did not isolate the reduced product, but conducted a rapid scan of multiple reaction conditions. With our initial efforts conducted at 100 °C, we commenced our evaluation at this temperature and reduced the H_2 pressure. The reaction flow rate was fixed at 1.0 mL/min. Table 1, entries 1–6; stepped the hydrogen pressure downwards in 10 bar increments at a constant 100 °C, and it is clear from the data presented that all H_2 pressures evaluated gave the desired product. Next we fixed the H_2 pressure at 100 bar and stepped the reaction temperature down in 10 °C increments from 90 to 40 °C. Here no product was observed at 40 or 50 °C, but a low conversion of 5% was noted at 60 °C (Table 1, entries 7–12).

Having rapidly surveyed the hydrogenation condition requirements for the phenyl analogue (**5a**), we applied the mildest full conversion conditions of 60 °C and 50 bar H_2 pressure to the series of acrylonitrile analogues of interest (**3a–e**; see Scheme 1 and Table 2 for details). In this series of experiments the reaction was allowed to continue uninterrupted for ca. 20 min, which ensured the collection of sufficient sample for purification, identification and yield calculations. As can be seen from Table 2, only the parent (*Z*)-2-phenyl-3-(1*H*-pyrrol-2-yl)acrylonitrile (**3a**) was converted quantitatively into the desired 2-phenyl-3-(1*H*-pyrrol-2-yl)propan-1-amine (**5a**) under these conditions. Poor conversion of the other analogues was noted, ranging from 23% (Table 2, entry 3) to 66% (Table 2, entry 4). We also noted simultaneous reduction of the aromatic NO_2 moiety to NH_2 under these conditions (Table 2, entry 3). The failure to achieve complete conversion into the bis-aromatic amines significantly complicated product isolation and purification.

Given the poor yields observed and the low conversion rates we initiated an additional evaluation and optimisation cycle. Repeating the flow reduction of **3a–e** (as 0.05 M solutions) in 1 M NH_3/MeOH at 70 bar H_2 pressure, 70 °C and 1.0 (or 0.5) mL/min allowed complete conversion of the α,β-unsaturated nitriles into the desired bis-aromatic amines (**5a–e**, Table 3).[24]

To demonstrate further the versatility of our approach, bis-aromatic amines **5a** and **5c** were dissolved in acetone (as 0.05 M solutions) and subjected to flow hydrogenation conditions in the presence of 5,6-dehydronorcantharidin (**6**) which gave the corresponding ring-opened acid amides **7** and **8** (Scheme 2). These compounds proved to be effective protein phosphatase 1 and 2A inhibitors (see Scheme 2 for data). This demonstrated the versatility of flow chemistry approaches to the rapid development of biologically active molecules.

In conclusion we have reported an elegantly simple flow chemistry approach to a series of bis-aromatic amines **5a–e** that have been further utilised in the development of novel norcantharidin derivatives **7** and **8**. Judicious choice of hydrogenation catalyst allows the reduction of either the olefin double bond (10% Pd-C) (**4a–e**) or reduction of the α,β-unsaturated nitrile (Raney Nickel) (**5a–e**). The

use of flow chemistry approaches allowed rapid surveying of the reaction conditions and the ability to up-scale the quantity of the product produced by simply increasing the reaction time.

Acknowledgements

The authors acknowledge the financial support of the Australian Research Council, the Australian Cancer Research and Ramaciotti Foundations, and John Morris Scientific, Australia. M.T. acknowledges the UNI-PRS postgraduate funding from the University of Newcastle. Protein phosphatase inhibition data for 7 and 8 were determined by Drs Jennette Sakoff and Jayne Gilbert, Calvary Mater Hospital, Newcastle Australia.

References and notes

1. McCluskey, A.; Sim, A. T. R.; Sakoff, J. A. *J. Med. Chem.* **2002**, *45*, 1151–1175.
2. Hill, T. A.; McGeachie, A. B.; Gordon, C. P.; Odell, L. R.; Chau, N.; Robinson, P. J.; McCluskey, A. *J. Med. Chem.* **2010**, *53*, 4094–4102.
3. Hill, T. A.; Gordon, C. P.; McGeachie, A. B.; Venn-Brown, B.; Odell, L. R.; Chau, N.; Quan, A.; Mariana, A.; Sakoff, J. A.; Chircop, M.; Robinson, P. J.; McCluskey, A. *J. Med. Chem.* **2009**, *52*, 3762–3773.
4. Colombo, M.; Peretto, I. *Drug Discovery Today* **2008**, *13*, 677–684.
5. Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 4017–4021.
6. Palmieri, P.; Ley, S. V.; Hammond, K.; Polyzos, A.; Baxendale, I. R. *Tetrahedron Lett.* **2009**, *50*, 3287–3289.
7. Ley, S. V.; Baxendale, I. R. *Chimia* **2008**, *62*, 162–168.
8. Smith, C. J.; Iglesias-Sigüenza, F. J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 2758–2761.
9. Stazi, F.; Cancogni, D.; Turco, L.; Westerduin, P.; Bacchi, S. *Tetrahedron Lett.* **2010**, *51*, 5385–5387.
10. Ali, A.; Bliese, M.; Rasmussen, J.-A. M.; Sargent, R. M.; Saubern, S.; Sawutz, D. G.; Wilkie, J. S.; Winkler, D. A.; Winzenberg, K. N.; Woodgate, R. C. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 993–997.
11. Tarleton, M.; Gilbert, J.; Robertson, M. J.; McCluskey, A.; Sakoff, J. A. *Med. Chem. Commun.* **2011**, *2*, 31–37.
12. Jautze, S.; Peters, R. *Synthesis* **2010**, 365–388.
13. Wang, K.; Kim, D.; Dömling, A. *J. Comb. Chem.* **2010**, *12*, 111–118.
14. Radi, M.; Botta, L.; Casaluce, G.; Bernardini, M.; Botta, M. *J. Comb. Chem.* **2010**, *12*, 200–205.
15. Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. *Org. Lett.* **2009**, *11*, 45–48.
16. Sonawane, Y. A.; Phadtare, S. B.; Borse, B. N.; Jagtap, A. R.; Shankarling, G. S. *Org. Lett.* **2010**, *12*, 1456–1459.
17. Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Pipko, S. E.; Shivanyuk, A. N.; Tolmachev, A. A. *J. Comb. Chem.* **2007**, *9*, 1073–1078.
18. McCluskey, A.; Robinson, P. J.; Hill, T.; Scott, J. L.; Edwards, J. K. *Tetrahedron Lett.* **2002**, *43*, 3117–3120.
19. Correa, W. H.; Edwards, J. K.; McCluskey, A.; McKinnon, I.; Scott, J. L. *Green Chem.* **2003**, *5*, 30–33.
20. **Example synthesis of pyrrole-2-ylacrylonitriles**: *(Z)-2-Phenyl-3-(1H-pyrrol-2-yl)acrylonitrile* (**3a**):[10] 1*H*-Pyrrole-2-carbaldehyde (**1**) (165 mg, 1.74 mmol) was added to vigorously stirred H_2O (10 mL) and heated to 50 °C upon which it dissolved. Phenylacetonitrile (**2a**) (193 mg, 1.65 mmol) was then slowly added forming a suspension. Heating was continued at 50 °C and once a clear solution was evident, typically 5–10 min, 40% $PhCH_2NMe_3(OH)$ (7 mL) was added dropwise. The reaction vessel was sealed and the mixture stirred at 50 °C for 5 h, the solution filtered hot, washed with warm H_2O and dried under suction and recrystallised from EtOH to afford **3a** as a brown solid; 73%; mp 94–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.57 (m, 2H), 7.45–7.40 (m, 2H), 7.42 (s, 1H), 7.35–7.30 (m, 1H), 7.08–7.06 (m, 1H), 6.73 (dd, J = 1.4, 3.7 Hz, 1H), 6.37 (dd, J = 1.4, 3.7, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 133.4, 130.7, 128.5, 127.6, 127.2, 124.4, 123.5, 120.1, 118.5, 110.3, 100.8.
21. Clapham, B.; Wilson, N. S.; Michmerhuizen, M. J.; Blanchard, D. P.; Dingle, D. M.; Nemcek, T. A.; Pan, J. Y.; Sauer, D. R. *J. Comb. Chem.* **2008**, *10*, 88–93.
22. Available from http://www.thalesnano.com (accessed Nov 2010).
23. **Example reduction of the olefin moiety**: *2-Phenyl-3-(1H-pyrrol-2-yl)propanenitrile* (**4a**):[11] (*Z*)-2-Phenyl-3-(1*H*-pyrrol-2-yl)acrylonitrile (**3a**) (990 mg, 5.1 mmol) was dissolved in sufficient freshly distilled dry acetone (100 mL) to form a 0.05 M solution. This solution was hydrogenated using the ThalesNano H-cube™ using a 10% Pd/C catalyst at 1 mL/min flow rate, 50 °C and 50 bar H_2 pressure. The acetone was removed in vacuo and the crude oil was subjected to flash silica chromatography (1:1 $CHCl_3$/hexanes) to afford **4a** as a brown oil; 98%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03 (br s, 1H), 7.42–7.35 (m, 3H), 7.29–7.26 (m, 2H), 6.69–6.67 (m, 1H), 6.15–6.13 (m, 1H), 6.03–6.02 (m, 1H), 4.01 (t, J = 7.4 Hz, 1H), 3.28–3.14 (m, 2H). ^{13}C NMR ($CDCl_3$,75 MHz): δ 134.5, 128.6, 127.8, 126.8, 125.7, 120.4, 117.3, 108.1, 107.4, 38.4, 34.0.
24. **Example reduction of the olefin and nitrile moieties**: *2-(4-Fluorophenyl)-3-(1H-pyrrol-2-yl)propan-1-amine* (**5c**): a solution of (*Z*)-2-(4-fluorophenyl)-3-(1*H*-pyrrol-2-yl)acrylonitrile **(3c)** (0.05 M, 990 mg, 4.6 mmol) in 1 M NH_3 in MeOH (100 mL) was hydrogenated using the ThalesNano H-cube™ using a Ra/Ni catalyst at 0.5 mL/min flow rate, 70 °C and 70 bar H_2 pressure. The solvent was removed in vacuo and the crude oil subjected to flash silica chromatography (0.05:0.95 MeOH/CH_2Cl_2) to afford **5c** as a clear oil; 100%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.47 (br s, 1H), 7.15–7.10 (m, 2H), 7.04–6.98 (m, 2H), 6.59–6.58 (m, 1H), 6.08–6.06 (m, 1H), 5.84–5.83 (m, 1H), 2.97–2.85 (m, 5H), 2.41 (br s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.8, 159.5, 138.0, 129.2, 128.7, 116.0, 115.1, 114.9, 107.5, 105.9, 47.9, 46.2, 32.0; HRMS calculated for $(M+H^+)$: $C_{13}H_{16}FN_2$, 219.1298; found 219.1307.