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Expanding the Utility of Flow Hydrogenation – A Robust Protocol Restricting Hydrodehalogenation

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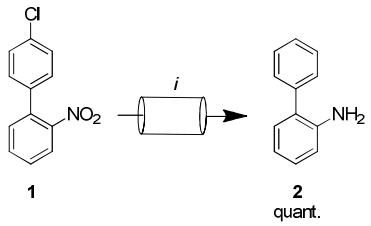
A commonly observed limitation of conducting hydrogenations under flow chemistry conditions is hydrodehalogenation. In a bid to circumvent this limitation a series of hydrogenation catalysts were screened, with 5 % Pt/C (sulfided) catalyst identified as an effective catalyst to selectively effect reductive aminations, nitro reduction, and alkene reductions in the presence of halogen atoms. Additionally the optimised protocol to effect reductive aminations, which utilised the ThalesNano H-cube pro™, cleanly reduced an imine functionality in the presence of a furan moiety indicating potential amenability with other labile functionalities.

Introduction

Over the past decade there has been an increasing body of evidence that flow hydrogenation significantly enhances the outcomes of a wide range of reduction based transformations.[1-6] Many of the key advantages of flow hydrogenation reaction systems, such as the H-Cube pro™, are attributed to the unique solid-liquid-gas triphasic reaction conditions along with the precise control of reaction parameters such as temperature, pressure, and catalyst exposure.[2,4,7] However, while flow hydrogenation provides numerous benefits over traditional batch approaches, a common and significant limitation is hydrodehalogenation.[4]

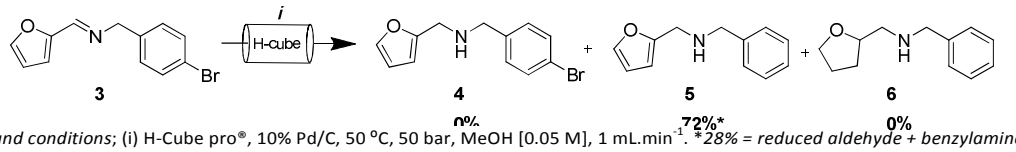
Hydrodehalogenation has been observed with a variety of palladium, rhodium, and nickel based heterogeneous catalysts which are commonly employed in flow hydrogenation.[4,8,9] As an example, the use of the ThalesNano H-cube pro™ (H-cube) charged with a 10% Pd/C has been reported to effect dual nitro reduction and dehalogenation of **1** to furnish compound **2** (Scheme 1).[4,10] Thus, whilst flow hydrogenation provides expeditious access to various dehalogenated analogues, it can be equally problematic if the halogen moiety is required for further synthetic manipulations.



Scheme 1: *Reagents and conditions*; (i) H-Cube®, 10 % Pd/C, 40 °C, 50 bar H_2, MeOH [0.1 M], 1 mL.min^{-1}

An obvious route to circumvent this issue is the use of metal hydride based batch methods such as Bu_3SnH or $Na(OAc)_3BH$, which can be time consuming requiring lengthy workup and purification. Here, flow chemistry protocols using immobilised reagents can be advantageous as catalysts can be readily portioned from reaction mixtures which significantly simplifies reaction workups and reduces the probability of heavy metal leaching.[11–17]

In our drug discovery efforts we have noted rapid hydrodehalogenation during the synthesis of a number of key intermediates. For example, in developing Diels-Alder adduct precursors, the reductive amination of 1-(4-bromophenyl)-*N*-(furan-2-ylmethylene)methanamine (**3**) with 10% Pd/C effected concurrent imine reduction and dehalogenation to yield **5**, or under alternative conditions resulted in global furan reduction, imine reduction, and dehalogenation (compound **6**, Scheme 2).[5] Thus we sought to develop a flow hydrogenation protocol which was amenable with halogenated materials.



Scheme 2: *Reagents and conditions*; (i) H-Cube pro®, 10% Pd/C, 50 °C, 50 bar, MeOH [0.05 M], 1 mL.min^{-1}. **28% = reduced aldehyde + benzylamine.*[5]

Results and Discussion

To date there are few reports of halogen retention under flow hydrogenation conditions.[10,18] Our initial investigations focused on a range of commercially available pre-packed immobilised catalysts (see Table 1 for details) and three aryl bromides; 4-bromoanisole (**7**), 4-bromoacetophenone (**8**), and 6-bromo-1*H*-indole (**9**) (Figure 1). Each aryl bromide was subjected to typical H-cube reduction conditions with a flow rate 1 mL.min^{-1}, at 50 °C, under 50 bar, and 100 % H_2 production.[5,19]

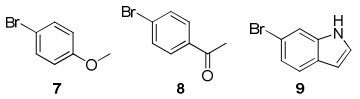
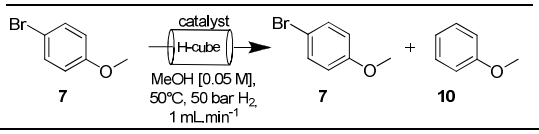


Figure 1: Three commercially available aryl bromides; 4-bromoanisole (**7**), 4-bromoacetophenone (**8**) and 6-bromo-1*H*-indole (**9**), investigated in the initial flow reduction hydrodehalogenation investigation.

Initially, as outlined in Table 1, treatment of a 0.05 M 4-bromoanisole (**7**) in MeOH under flow hydrogenation conditions was examined with a range of heterogeneous catalysts. Pd-based catalysts effected high levels of hydrodebromination to **10** from 50% (Table 1, entry 3); 20% $Pd(OH)_2/C$) to 62% (Table 1, entry 1; 10% Pd/C). High levels of hydrodebromination were also noted with RuO_2 (87%; Table 1, entry 4) and RaNi (23%; Table 1, entry 5), dropping to 6% with 5% Rh/C (Table 1, entry 6). However, the remaining catalysts examined displayed non-detectable levels of hydrodehalogenation (Table 1, entries 7-11).

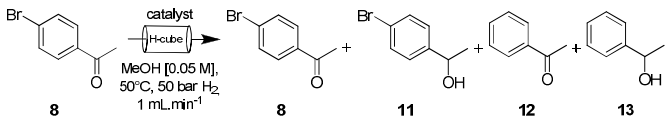
Table 1: Evaluation of commercially available catalysts for the hydrogenation of **7** at 1.0 mL.min^{-1} flow rate, 50 °C, 50 bar H_2. Percent conversions were determined by GC-MS analysis.



Entry	Catalyst	Conversion (peak area %) 7	10
1	10% Pd/C	38	62
2	Pd Tetrakis	40	60
3	20% $Pd(OH)_2/C$	50	50
4	RuO_2	13	87
5	RaNi	77	23
6	5% Rh/C	94	6
7	5% Rh/Al_2O_3	100	0
8	5% Pt/C (sulfided)	100	0
9	5% Re/C	100	0
10	Re_2O_7	100	0
11	0.5% Ir/C	100	0

With 4-bromoacetophenone (**8**) we observed similar outcomes (Table 2). Pd-based catalysts and RuO_2 resulted in a significant level of dehalogenation and in a number of cases, carbonyl reduction (e.g. Table 2, entries 1-4). Rhodium-based catalysts elicited a comparable outcome (Table 2, entries 6 and 7) while 5% Pt/C (sulfided) afforded negligible amounts of **12** or **13** (Table 2, entry 8). Interestingly, RaNi promoted formation of the carbonyl reduced product **11** with retention of the bromine moiety in addition to **12** (Table 2, entry 5), whereas neither Re- nor Ir- catalysts afforded detectable amounts of the reduced or hydrodehalogenated products (Table 2, entries 9-11).

Table 2: Evaluation of commercially available catalysts for the hydrogenation of **8** at 1.0 mL/min flow rate, 50ºC, 50 bar H_2. Percent conversions were determined by GC-MS analysis.

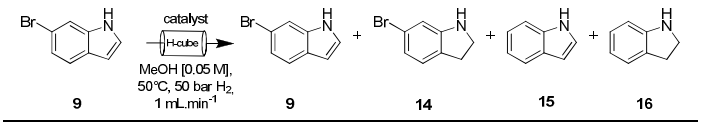


8 8 11 12 13

Entry	Catalyst	Conversion (peak area %)			
		8	11	12	13
1	10% Pd/C	0	0	15	85
2	Pd Tetrakis	6	0	83	11
3	20% Pd $(OH)_2$/C	0	0	31	69
4	RuO_2	0	0	42	58
5	RaNi	40	15	45	0
6	5% Rh/C	66	3	0	31
7	5% Rh/Al_2O_3	42	2	0	56
8	5% Pt/C (sulfided)	87	0	7	6
9	5% Re/C	100	0	0	0
10	Re_2O_7	100	0	0	0
11	0.5% Ir/C	100	0	0	0

Subjecting 6-bromoindole (**9**) to our typical flow reduction conditions again yielded similar outcomes with each of the Pd-based catalysts effecting a significant amount of dehalogenation to afford compound **15**, in addition to the reduced product **16** (Table 3). Likewise the RuO_2, and RaNi, catalysts promoted a significant amount of dehalogenation along with **16**. Interestingly, in contrast to the previous studies, the Rh-based catalyst effected a minimal amount of dehalogenation (Table 3, entries 6 and 7). As previously noted with **7** and **8**, 5% Pt/C (sulfided), the Re-based catalysts, and the 0.5 % Ir/C catalyst each effected negligible to non-detectable levels of dehalogenation.

Table 3: Evaluation of hydrogenation catalysts for the dehalogenation of **9** to a range of products (**14** - **16**) at 1.0 mL.min^{-1} flow rate, 50ºC, 50 bar H_2. Percent conversions were determined by GC-MS analysis.

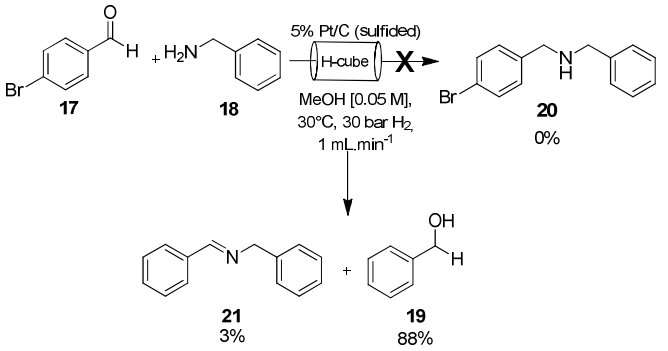


9 9 14 15 16

Entry	Catalyst	Conversion (peak area %)			
		9	14	15	16
1	10% Pd/C	6	0	87	7
2	Pd Tetrakis	24	0	70	6
3	20% Pd $(OH)_2$/C	0	0	57	43
4	RuO_2	8	0	69	23
5	RaNi	57	0	36	7
6	5% Rh/C	89	2	7	2
7	5% Rh/Al_2O_3	99	0	1	0
8	5% Pt/C (sulfided)	97	0	3	0
9	5% Re/C	100	0	0	0
10	Re_2O_7	100	0	0	0
11	0.5% Ir/C	100	0	0	0

From these initial investigations 5 % Pt/C (sulfided), 5 % Re/C, Re_2O_7, and 0.5 % Ir/C catalysts presented as the most viable catalysts for further examination in reductive amination and nitro reductions, in the presence of a bromine atom. However, of these catalysts we noted that 5% Pt/C did display very low levels of dehalogenation (Table 3, entry 8) in addition to carbonyl reduction (Table 2, entry 8) suggesting that of the aforementioned catalysts it may be the superior to promote hydrogenation reactions.

Commencing with the 5% Pt/C (sulfided) catalyst we examined the reductive amination of 4-bromobenzaldehyde (**17**) with benzylamine (**18**) (Scheme 3). Reactions were conducted using 0.05 M methanolic solutions of **17** and **18**, under 30 bar H_2 pressure, 30 ºC and a flow rate of 1 mL.min^{-1}. GC-MS analysis of the resulting mixture revealed a significant level of aldehyde reduction and hydrodebormination to benzyl alcohol (**19**; 88%) with imine **21** as sole additional product. No evidence of the desired amine, **20** was observed.

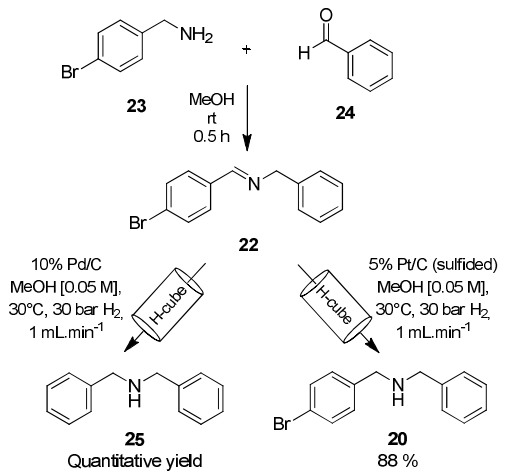


Scheme 3: Attempted synthesis of N-benzyl-1-(4-bromophenyl)methanamine (**20**).

Consequently, in an effort to minimise initial carbonyl reduction we examined the effect of imine (**22**) pre-formation by allowing a methanolic solution of **17** and **18** to stand at room temperature for half an hour prior to hydrogenation catalyst exposure (Scheme 4).[19] After this time, the solution was subjected to the flow reduction conditions outlined above with 5% Pt/C (sulfided) as the catalyst. Pre-forming **22** allowed subsequent reduction and isolation of the desired amine (**20**) in an 82% yield with the debrominated analogue a minor product (~15%).

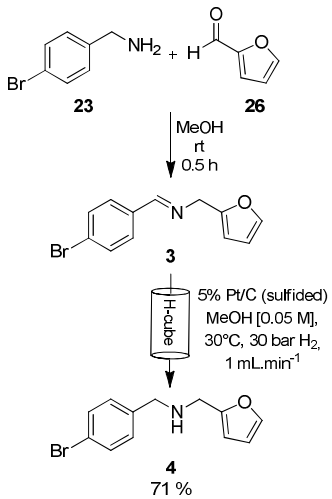
Scheme 4: Synthesis of *N*-benzyl-1-(4-bromophenyl)methanamine (**20**) *via* pre-formation of the imine **(22).**

Application of this imine pre-formation approach was equally effective for the formation of **20** using 4-bromobenylamine (**23**) and benzaldehyde (**24**) affording **20** in an 88 % yield. In contrast this approach with 10 % Pd/C catalyst gave **25**, a result of quantitative imine reduction and hydrodebromination (Scheme 5). A similar outcome was noted commencing with 4-chlorobenzylamine. Using the 5 % Pt/C (sulfided) catalyst facilitated reduction and halogen retention (90% yield) whereas the 10 % Pd/C catalyst gave the reduced and hydrodechlorinated product.



Scheme 5: Alternative synthesis to access **20**, whereby 4-bromobenzylamine (**23**) and benzaldehyde (**24**) were initially reacted at room temperature to afford the imine **22**. Hydrogenation of imine **22** with 5% Pt/C (sulfided) afforded the desired analogue **20**, whereas hydrogenation with 10% Pd/C afforded the dehalogenated analogue **25.**

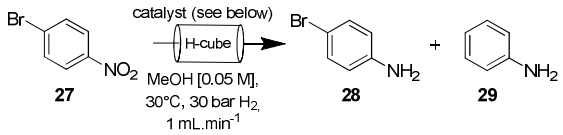
With the 5% Pt/C (sulfidied) catalyst proving effective in the retention of both bromine and chlorine atoms we next sought to expand this approach to additional labile moieties. Previously we have demonstrated that the furan component of compound **3** was particularly susceptible to reduction under flow hydrogenation conditions with a range of Pd-based catalysts (Scheme 2).[5] However 5 % Pt/C (sulfided) cleanly catalysed the reductive amination of 4-bromobenzylamine with furfural to furnish **4** in a 71 % yield (Scheme 6).



Scheme 6: Synthesis of *N*-(4-bromobenzyl)-1-(furan-2-yl)methanamine (**4**).

Our attention subsequently turned to nitro reduction as while a number of NO_2 to NH_2 flow reduction protocols have recently been reported,[2,4,20] there is a paucity of established protocols utilising halogenated materials. The majority of reported nitro reduction methods utilise 10% Pd/C or RaNi which typically promote quantitative dehalogenation,[4,10,20] while the H-cube application notes recommend 10 % Pd/C or RuO_2.[4,20,21] Given our previous findings, and the lack of prior reports, our investigations commenced with 5% Pt/C (sulfided). As before, a 0.05 M methanolic solution of 1-bromo-4-nitrobenze (**27**) was flow hydrogenated at 30 ºC, 30 bar H_2 and 1 ml.min^{-1} and the outcome of this reduction benchmarked against 10% Pd/C and RuO_2 (Table 4).

Table 4: Evaluation of hydrogenation catalysts for selective nitro reduction, conditions were 1.0 mL.min^{-1} flow rate, 30ºC, 30 bar H_2. Percent conversions were determined by GC-MS analysis.

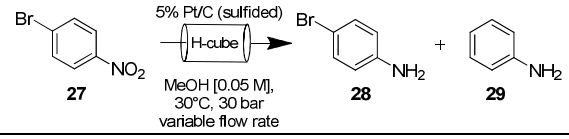


Entry	Catalyst	Conversion (peak area %)		
		27	28	29
1	5% Pt/C (sulfided)	0	85	15
2	10% Pd/C	0	0	100
3	RuO_2	0	20	80

As anticipated, the 10% Pd/C and RuO_2 catalysts promoted concurrent nitro reduction and hydrodehalogenation affording aniline in 100 and 80% conversion respectively (Table 4, entries 2 and 3). The RuO_2 catalyst gave **28** in a modest 20% conversion. The use of 5% Pt/C (sulfided) was considerably more effective, yielding **28** in an 85% yield (Table 4, entry 1).

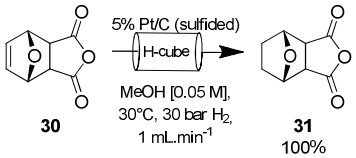
Given our previous experiences with the selective flow reduction of furan moieties,[5] we hypothesised that increased flow rates (i.e. reduced catalyst exposure) coupled with increases in H_2 pressure would effect a superior reaction outcome. As anticipated (Table 5), a reduction in residence time (increased flow rate) afforded **28** in a 90% yield at 3 mL.min^{-1}.

Table 5: Evaluation of residence time for selective nitro reduction, conditions set to 30ºC, 30 bar H_2, 100% H_2, and variable flow rate. Percent conversions were determined by GC-MS analysis.



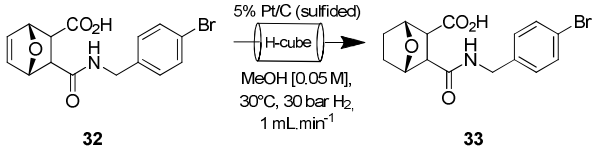
Entry	Residence Time in Min (flow rate)	H_2 (%)	Conversion (peak area %)		
			27	28	29
1	0.37 (1 mL.min^{-1})	100	0	85	15
2	0.19 (2 mL.min^{-1})	100	0	88	12
3	0.13 (3 mL.min^{-1})	100	0	90	10

To validate the use of 5% Pt/C (sulfided) as a robust protocol for the reduction of compounds with labile moieties we were eager to investigate the utility of this procedure in a drug development program. Specifically the synthesis of norcantharidin analogues which we are currently developing as protein phosphatase inhibitors.[5,22] Here we examined the treatment of 5,6-dehydronorcantharidin (**30**) at 1 mL.min^{-1}, 30 ºC and 30 bar H_2 pressure. This effected quantitative conversion to norcantharidin (**31**) in a quantitative yield (Scheme 7).



Scheme 7: Synthesis of norcantharidin *via* the reduction 5,6-norcantharidin.

As an extension the protocol also cleanly effected olefin reduction in **32** with a 0.05 M solution in methanol/acetone (1:1) [0.05 M] at 1 mL.min^{-1}, 30 ºC and 30 bar H_2 pressure affording **33** in a quantitative conversion (Scheme 8).



Scheme 8: Synthesis of 3-((4-bromobenzyl)carbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (**33**) from the 5,6-norcanthardin analogue (**32**).

Conclusions

To date, hydrodehalogenation has represented a significant limitation of flow hydrogenation. To this end we have established a robust protocol utilising 5 % Pt/C (sulfided) to effect reductive amination, nitro reduction, and alkene reduction in the presence of halogen atoms in addition to furan moieties which we have previously demonstrated to be highly susceptible to reduction. Thus, this protocol circumvents one of the significant limitations of flow hydrogenation and we are currently investigating the methodology in the development of extended compound libraries which will be reported in due course.

Experimental

General experimental

All reagents were purchased from Sigma Aldrich and were used without purification, with the exception of furfural, which was distilled from glass prior to use. Solvents were bulk, and distilled from glass prior to use.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance™ AMX 400 MHz spectrometer at 400.13 and 100.62 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) measured to relative the internal standards. Coupling constants (*J*) are expressed in Hertz (Hz). Mass spectra were recorded on a Shimadzu LCMS 2010 EV using a mobile phase of 1:1 acetonitrile:H_2O with 0.1 % formic acid. Gas chromatography-mass spectrometry (GC-MS) was performed on a Shimadzu GC-MS QF2010 EI/NCI System equipped with a ZB-5MS capillary column of 5% phenyl-arylene stationary phase.

Melting points were recorded on a BUCHI Melting Point M-565 and are uncorrected. IR spectra were recorded on a PerkinElmer Spectrum Two™ FTIR Spectrometer. Thin layer chromatography (TLC) was performed on Merck 60 F_{254} pre-coated aluminium plates with a thickness of 0.2 mm. Column chromatography was performed under 'flash' conditions on Merck silica gel 60 (230-400 mesh).

Hydrogenations were performed either using a ThalesNano H-Cube™ or a ThalesNano H-CubePro™ (H-Cube™) continuous-flow hydrogenation reactor. All reactions were passed through the H-Cube™ reactor once, unless otherwise specified.

General Procedure 1 – Direct Reductive Amination

***N*-benzyl-1-(4-bromophenyl)methanamine (20)**

A solution of 4-bromobenzylamine (23) (0.18 g, 0.94 mmol) and benzaldehyde (24) (0.1 mL, 0.94 mmol) was diluted in MeOH (19 mL) to afford a 0.05 M solution which was subsequently hydrogenated with a H-Cube™ using a 5% Pt/C catalyst at 1 mL.min^{-1} flow rate, 30°C and 30 bar H_2 pressure. After completion of the reaction, the solvent was removed in vacuo and the resulting crude oil was subjected to flash silica chromatography (1:9 MeOH:DCM) to afford 20 as a clear oil (0.21 g, 82 %). LRMS (ESI$^+$) m/z 277 (M+1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.44 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.31 (m, 4H), 7.26 – 7.20 (m, 3H), 3.78 (s, 2H), 3.75 (s, 2H), 1.63 (s, NH). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.7, 140.1, 139.4, 131.5, 129.9, 128.5, 128.1, 127.1, 120.7, 53.1, 52.4.

***N*-(4-bromobenzyl)-1-(furan-2-yl)methanamine (4).** A solution of 4-bromobenzylamine (**23**) (0.10 g, 0.54 mmol) and furfural (**26**) (0.04 mL, 0.54 mmol) was diluted in MeOH (11 mL) to afford a 0.05 M solution which was subsequently hydrogenated with a H-Cube™ using a 5% Pt/C catalyst at 1 mL.min^{-1} flow rate, 30°C and 30 bar H_2 pressure. After completion of the reaction, the solvent was removed in vacuo and the resulting crude oil was subjected to flash silica chromatography (1:9 MeOH:DCM) to afford **4** as a yellow oil (0.1 g, 71 %). LRMS (ESI$^+$) m/z 267 (M+1). ^{1}H NMR (Acetone, 400 MHz): δ 7.49 – 7.46 (m, 2H), 7.45 (dd, J = 1.9, 0.8 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 6.35 (dd, J = 2.9, 1.9 Hz, 1H), 6.26 – 6.22 (m, 1H), 3.74 (s, 2H), 3.72 (s, 2H). ^{13}C NMR (Acetone, 101 MHz): δ 155.7, 154.6, 141.6, 131.1, 130.1, 119.8, 110.1, 106.6, 51.5, 45.0.

General Procedure 2 – Nitro Reduction

4-Bromoanilie (29). A solution of 1-bromo-4-nitrobenzene (**27**) (0.15 g, 0.74 mmol) was diluted in MeOH (15 mL) to afford a 0.05 M solution which was subsequently hydrogenated with a H-Cube™ using a 5% Pt/C (sulfided) catalyst at 1 mL.min^{-1} flow rate, 30°C and 30 bar 10% H_2 pressure. After completion of the reaction, the solvent was removed *in vacuo* and the resulting crude oil was subjected to flash silica chromatography (1:9 EtOAc:Hexanes) to afford 4-bromoaniline **29** as a yellow oil (0.1 g, 83 %). LRMS (ESI$^+$) m/z 173 (M+1). ^{1}H NMR (Acetone, 400 MHz) δ 7.18 – 7.13 (m, 1H), 6.64 – 6.59 (m, 1H), 4.79 (s, 1H). ^{13}C NMR (Acetone, 101 MHz): δ 147.9, 131.5, 116.1, 107.3.

General Procedure 3 - Alkene Reduction

Norcantharidin (31). A solution of 5,6-norcantharidin (**30**) (0.20 g, 1.2 mmol) was diluted in MeOH (24 mL) to afford a 0.05 M solution which was subsequently hydrogenated with a H-Cube™ using a 5% Pt/C (sulfided) catalyst at 1 mL.min^{-1} flow rate, 30°C and 30 bar 10% H_2 pressure. After completion of the reaction, the solvent was removed *in vacuo* to afford norcantharidin 31 as a white solid (0.20 g, 100%); mp 115 °C. LRMS (ESI$^+$) m/z 267 (M+1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.06 (dd, *J* = 3.2, 2.2 Hz, 1H), 3.20 (s, 1H), 1.99 – 1.83 (m, 1H), 1.75 – 1.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.15, 80.18, 50.58, 28.15.

3-((4-bromobenzyl)carbamoyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (33). 5,6-norcantharidin (**30**) (0.18 g, 1.07 mmol) and 4-bromobenzylamine (**23**) (0.2 g, 1.07 mmol) were dissolved separately in diethyl ether (10 mL x 2) and the solutions were added together and the reaction was left to stir at room temperature for 4 hours. The solution was filtered and washed with cold diethyl ether and dried under suction to afford **32** as a white solid. The crude product **32** (0.15 g, 0.74 mmol) was dissolved in a mixture (1:1) methanol:acetone (6 mL) to afford a 0.05 M solution which was subsequently hydrogenated with a H-Cube™ using a 5% Pt/C (sulfided) catalyst at 1 mL.min^{-1} flow rate, 30°C and 30 bar H_2 pressure. After completion of the reaction, the eluate was concentrated *in vacuo* and then triturated with ether to afford **33** as a white solid (0.32 g, overall 84 %); mp 180 - 181 °C. ^{1}H NMR (DMSO, 400 MHz) δ 11.96 (s, 1H), 8.05 (t, *J* = 5.8 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 4.74 (d, *J* = 3.4 Hz, 1H), 4.51 (d, *J* = 4.3 Hz, 1H), 4.22 (dd, *J* = 15.4, 6.0 Hz, 1H), 4.15 (dd, *J* = 15.4, 5.7 Hz, 1H), 2.92 (d, *J* = 9.7 Hz, 1H), 2.86 (d, *J* = 9.7 Hz, 1H), 1.63 – 1.41 (m, 4H).^{13}C NMR (DMSO, 101 MHz): δ 172.9, 172.1, 139.6, 131.5, 129.9, 120.1, 79.2, 77.2, 53.3, 51.8, 42.0, 29.4, 28.9.

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Supporting Information Available: Supplementary data (GS MS chromatographic traces, ^{1}H and ^{13}C NMR spectra) associated with this article can be found in the online version at: doi:xxxxxxxxx.

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