Expedient Reductive Amination of Aldehyde Bisulfite Adducts

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Abstract: A novel, one-pot protocol for the direct reductive amination of aldehyde bisulfite adducts is reported. Bisulfite adducts of aliphatic and aromatic aldehydes, on treatment with an organic base under non-aqueous conditions liberate the aldehyde in situ, which then undergoes efficient reductive amination with amines in the presence of sodium triacetoxyborohydride.

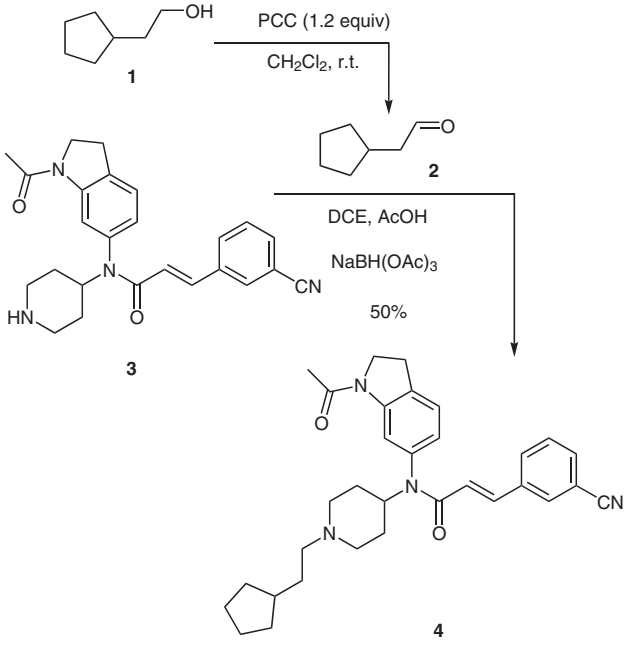
Key words: Bisulfite adducts, reductive amination, sodium triacetoxyborohydride

Bisulfite adducts provide a means for the isolation and or separation of carbonyl compounds from compounds not having this functional group. These adducts are generally crystalline solids that are easy to handle and are stable for prolonged periods of time. However, reports of their use in synthetic applications are sparse. This may be due to the fact that regeneration of aldehydes from their bisulfite adducts is typically carried out by treatment with aqueous acid[1] or base,[2] conditions which may not be tolerated by many aldehydes or other functional groups present. To solve this problem, a novel method for the regeneration of aldehydes from bisulfite adducts using chlorotrimethylsilane was reported by Kjell et al.[3] This suggests that aldehydes can be regenerated in situ in organic solvents under non-aqueous conditions, and that the bisulfite adducts themselves can presumably be used as an aldehyde surrogate in synthetic applications. Reductive amination reactions are well precedented in synthetic organic chemistry due to their versatility.[4] It is a process by which aldehydes or ketones are transformed into amines, which are useful intermediates for the synthesis of agrochemicals and pharmaceuticals. A variety of aldehydes have been used in reductive aminations. More recently, the utility of an aldehyde bisulfite adduct in a reductive amination reaction was disclosed, albeit in lower yield than the comparable reductive amination with the free aldehyde.[5] In this report, one equivalent of the trifluoroacetate salt of an amine was reacted with a bisulfite adduct (1.5 equivalents) with azeotropic removal of water and subsequent reduction of the iminium intermediate with sodium triacetoxyborohydride. Herein, we report a simple, high-yielding one-pot protocol for the direct reductive amination of aldehyde bisulfite adducts.

As part of a medicinal chemistry program, a series of piperidinylindoline cinnamides was prepared, the representatives of which were identified as the first potent, non-peptide, low molecular weight selective neuropeptide Y Y_2 antagonists.[6,7] One of the compounds in the series, *trans*-*N*-(1-acetyl-2,3-dihydro-1*H*-indol-6-yl)-3-(3-cyanophenyl)-*N*-[1-(2-cyclopentylethyl)piperidin-4-yl]acrylamide (**4**) was selected for a detailed in vivo pharmacological evaluation of the role of Y_2 receptors in a variety of physiological conditions and thus, multi-gram quantities of **4** were required.

In the drug discovery synthesis of **4**, the key step (Scheme 1) was reductive amination of 2-cyclopentylacetaldehyde (**2**) with the functionalized indoline **3**. Aldehyde **2** was obtained by oxidation of commercially available 2-cyclopentylethanol (**1**). However, due to its volatility, isolation of **2** proved to be problematic as product loss was encountered upon extractive workup and rotary evaporation of the solvent. Thus, subsequent reductive amination with **3** was carried out with the organic extract of the reaction mixture containing crude **2**, to afford piperidinylindoline cinnamide **4** in ca. 50% yield.

For the scale-up synthesis, we sought to explore a practical process for the isolation of aldehyde **2**. As bisulfite adducts of aldehydes are known to be stable, crystalline



Scheme 1 Preparation of piperidinylindoline cinnamide **4**

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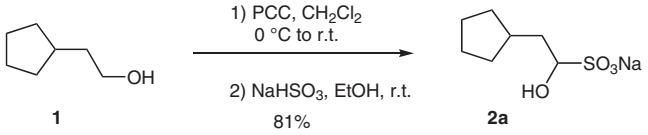
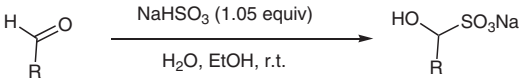
solids, isolation and storage of **2** in this form appeared attractive. Thus, after oxidation of **1** with pyridinium chlorochromate, the reaction mixture was decanted. The organic layer was diluted with ethanol and treated with an aqueous solution of sodium bisulfite (1.05 equivalents). Partial concentration of the reaction mixture resulted in precipitation of the bisulfite adduct **2a** in 81% yield (Scheme 2).



Scheme 2 Synthesis of bisulfite adduct **2a**

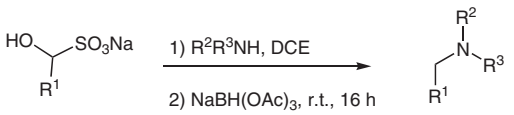
In order to investigate the potential of bisulfite adducts in direct reductive amination, a number of aldehyde bisulfite adducts were prepared in a similar manner by treating an ethanolic solution of the aldehyde with aqueous sodium bisulfite (Table 1). These adducts were obtained with good purity (>95%) and were used directly in our reductive amination experiments. Recrystallization from ethanol–water mixtures afforded analytically pure material.

Table 1 Preparation of Aldehyde Bisulfite Adducts



Entry	R	Yield (%) of product
1	Ph	92
2	4-EtC_6H_4	97
3	4-MeOC_6H_4	94
4	$PhCH_2CH_2$	89
5	cyclohexyl	90

Exploratory reductive amination reactions were carried out on five millimole scale at a concentration of 20 mL/g. Treatment of the bisulfite adduct of benzaldehyde with one equivalent of piperidine followed by sodium triacetoxyborohydride afforded, after workup, the corresponding tertiary amine product in 42% yield (Scheme 3 and Table 2, entry 1a).



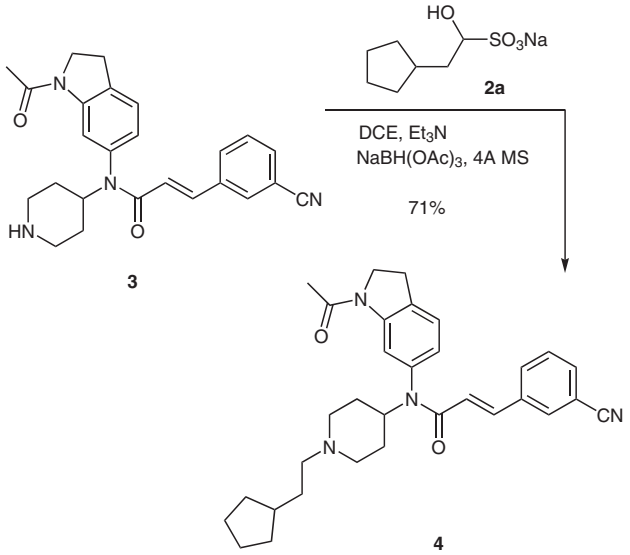
Scheme 3 Reductive amination of bisulfite adducts with various amines

We discovered that the use of two equivalents of piperidine (Table 2, entry 1b) resulted in a good yield of the corresponding tertiary amine product. Presumably, the first equivalent of piperidine liberates the aldehyde from the bisulfite adduct[8] in situ, and the second equivalent participates in the amination reaction.

In fact, while the ^{1}H NMR spectrum of the benzaldehyde bisulfite adduct (Table 1, entry 1) in dichloromethane-d_2 did not show a resonance due to the aldehyde proton, within five minutes of the addition of one equivalent of triethyl-d_{15}-amine, liberation of the aldehyde was complete, as was evident by the appearance of an aldehyde proton signal in the ^{1}H NMR spectrum. Although the reaction proceeds in solvents typically used for reductive aminations such as dichloromethane, dichloroethane and tetrahydrofuran, we preferred dichloroethane, as reactions in this solvent are reported to be faster.[9]

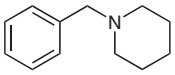
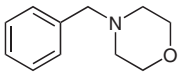
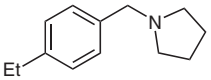
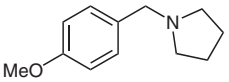
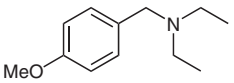
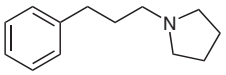
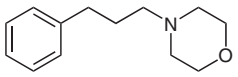
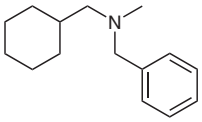
In order to extend the scope of the reaction, we explored the use of a tertiary amine (e.g., triethylamine) to liberate the aldehyde from its bisulfite adduct. Thus, the bisulfite adduct was first treated with triethylamine (1.1 equivalents), followed by piperidine (1.1 equivalents) and sodium triacetoxyborohydride (Table 2, entry 1c). Extractive workup followed by purification afforded the desired product in 94% yield. The generality of the method was evaluated by subjecting the bisulfite adducts to reductive amination conditions with various amines. In all cases, the reactions proceeded smoothly to afford, after purification, excellent isolated yields of the desired products (Table 2). While the yields of products from both methods are comparable, the latter method is particularly useful if the reacting amine is expensive or a product of a multi-step synthesis, and hence deemed non-expendable. Thus, the reductive amination in the synthesis of **4** was accomplished by treatment of the bisulfite adduct **2a** with triethylamine (one equivalent) followed by the amine **3** (0.9 equivalents). The reaction proceeded smoothly to produce the desired product in 71% isolated yield (Scheme 4).

In conclusion, we have demonstrated the utility of aldehyde bisulfite adducts in direct reductive amination reactions. This method is particularly attractive in cases where



Scheme 4 One-step synthesis of **4** via reductive amination

Table 2 Reductive Amination of Bisulfite Adducts with Various Amines

Entry	Bisulfite Adduct (R^1)	Amine (equiv)	Product[a]	Yield (%)
1a	Ph	piperidine (1.0)		42
1b	Ph	piperidine (2.0)		85
1c	Ph	Et_3N (1.1), piperidine (1.1)		94
1d	Ph	morpholine (2.0)		87
2a	4-EtC_6H_4	pyrrolidine (2.0)		84
2b	4-EtC_6H_4	Et_3N (1.1), pyrrolidine (1.1)		80
3a	4-$MeOC_6H_4$	Et_3N (1.1), pyrrolidine (1.1)		85
3b	4-$MeOC_6H_4$	Et_3N (1.1), diethylamine (1.1)		88
4a	$PhCH_2CH_2$	Et_3N (1.1), pyrrolidine (1.1)		80
4b	$PhCH_2CH_2$	Et_3N (1.1), morpholine (1.1)		83
5	cyclohexyl	Et_3N (1.1), *N*-methylbenzylamine (1.1)		79

[a] All products were purified using a general acid–base workup procedure and the purity was determined to be >98% by HPLC.

the aldehyde to be used in a reductive amination step is not easy to isolate or purify, or cannot be stored as such due to stability issues. Preparation of the aldehyde bisulfite adduct alleviates these problems and in addition, this derivative proves to be an excellent aldehyde surrogate in direct reductive amination reactions. A second distinct advantage with this method is the use of an organic base under non-aqueous conditions to liberate the aldehyde in situ. Thus, aldehyde bisulfite adducts with functional groups that may not withstand standard protocols of strong aqueous base or acid treatment for aldehyde regeneration can be handled with relative ease. The methodology has been applied to the synthesis of compound **4** resulting in improved yields in the isolation of an aldehyde intermediate as well as in the key reductive amination step. In addition to demonstrating the generality of this method, we have also applied this procedure for the synthesis of multi-gram quantities of other pharmaceutical intermediates.

All reactions were carried out under a positive pressure of N_2. 1,2-Dichloroethane (DCE) was dried by passing through activated alumina cylinders under Ar. Glassware was oven-dried and cooled to r.t. prior to use. Reaction mixtures and products were analyzed by reverse phase HPLC according to the following conditions: column, Zorbax Eclipse XBD-C8, 5 m, 4.6 × 1.50 mm; gradient, 1%–99% MeCN–H_2O containing 0.1 v/v TFA, 8 min; 99% MeCN–H_2O containing 0.1 v/v TFA, 2 min. Column chromatography was carried out on EMD Chemicals silica gel (230–400 mesh). Melting points were determined using an automated electrothermal instrument (OptiMelt, Stanford Research Systems). ^1H and ^{13}C NMR spectra were recorded using either a Bruker DPX 400 or a Bruker DRX 500 spectrometer (^1H at 400 or 500 MHz and ^{13}C at 100 MHz) in the solvents noted. HRMS for accurate mass analysis were performed using a Bruker micro TOF instrument (TOF ESI).

Aldehyde Bisulfite Adducts; General Procedure

To a stirred soln of the aldehyde (0.1 mol) in EtOH (200 mL) was added dropwise a soln of anhyd $NaHSO_3$ (10.6 g, 102.0 mmol) in H_2O (20 mL) over 0.5 h. The resulting suspension was stirred at ambient temperature for 16 h and subsequently at 0 °C for 4 h, following which the product was collected by filtration. The filter-cake was broken, washed with hexanes (3 × 100 mL) and dried in vacuo to afford the bisulfite adduct as a white powder. Recrystallization of a small sample from EtOH–H_2O furnished an analytically pure sample.

Sodium Hydroxy(phenyl)methanesulfonate (Table 1, Entry 1)

Yield: 92%; white plates; mp 153–156 °C (dec.).

^1H NMR (500 MHz, DMSO-d_6): δ = 7.50–7.38 (m, 2 H), 7.23–7.18 (m, 3 H), 5.81 (d, *J* = 5.2 Hz, 1 H), 4.96 (d, *J* = 5.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 140.5, 128.8, 127.8, 127.6, 85.9.

HRMS (TOF ESI): *m*/*z* $[M - Na]^-$ calcd for $C_7H_7O_4S$: 187.0071; found: 187.0076.

Sodium (4-Ethylphenyl)(hydroxy)methanesulfonate (Table 1, Entry 2)

Yield: 97%; white plates; mp 136–138 °C.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.33 (d, *J* = 6.1 Hz, 2 H), 7.06 (d, *J* = 6.1 Hz, 2 H), 5.68 (d, *J* = 5.1 Hz, 1 H), 4.90 (d, *J* = 5.1 Hz, 1 H), 2.59 (q, *J* = 7.5 Hz, 2 H), 1.18 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 142.9, 137.9, 128.7, 127.2, 85.8, 28.9, 16.8.

HRMS (TOF ESI): *m*/*z* [M – Na]$^-$ calcd for $C_9H_{11}O_4S$: 215.0384; found: 215.0381.

Anal. Calcd for $C_9H_{11}O_4NaS$: C, 45.37; H, 4.65; S, 13.46. Found: C, 45.10; H, 4.84; S, 13.89.

Sodium Hydroxy(4-methoxyphenyl)methanesulfonate (Table 1, Entry 3)

Yield: 94%; white plates; mp 155–157 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.35 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 5.69 (d, *J* = 5.1 Hz, 1 H), 4.90 (d, *J* = 5.2 Hz, 1 H), 3.73 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2, 132.7, 129.8, 113.2, 85.5, 55.9.

HRMS (TOF ESI): *m*/*z* [M – Na]$^-$ calcd for $C_8H_9O_5S$: 217.0176; found: 217.0167.

Anal. Calcd for $C_8H_9O_5NaS$: C, 40.00; H, 3.78; S, 13.35. Found: C, 39.64; H, 3.82; S, 12.97.

Sodium 1-Hydroxy-3-phenylpropane-1-sulfonate (Table 1, Entry 4)

Yield: 89%; white plates; mp 193–210 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.30–7.24 (m, 2 H), 7.20–7.14 (m, 3 H), 5.32 (d, *J* = 5.9 Hz, 1 H), 3.79 (ddd, *J* = 9.5, 6.0, 3.1 Hz, 1 H), 2.79–2.71 (m, 1 H), 2.63–2.55 (m, 1 H), 2.06–1.97 (m, 1 H), 1.74 (dtd, *J* = 14.4, 9.5, 9.5, 5.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 142.7, 128.7, 128.5, 125.9, 82.2, 34.2, 31.9.

HRMS (TOF ESI): *m*/*z* [M – Na]$^-$ calcd for $C_9H_{11}O_4S$: 215.0384; found: 215.0382.

Anal. Calcd for $C_9H_{11}O_4NaS$: C, 45.37; H, 4.65; S, 13.46. Found: C, 45.06; H, 4.77; S, 13.57.

Sodium Hydroxy(cyclohexyl)methanesulfonate (Table 1, Entry 5)

Yield 90%; white plates; mp 179–185 C (dec).

^{1}H NMR (DMSO-d_6, 500 MHz = 4.75 (d, *J* = 5.3 Hz, 1 H), 3.62 (t, *J* = 5.2 Hz, 1 H), 2.08–1.96 (m, 1 H), 1.82–1.50 (m, 5 H), 1.20–0.98 (m, 5 H).

^{13}C NMR (DMSO-d_6, 100 MHz): = 87.8, 31.5, 27.8, 27.1, 27.0, 26.7.

HRMS (TOF ESI): *m*/*z* [M – Na]$^-$ calcd for $C_7H_{13}O_4S$: 193.0540; found 193.0537.

Reductive Amination of Bisulfite Adducts; General Procedures

Method A: Using Two Equivalents of the Reacting Amine

A suspension of aldehyde bisulfite adduct (5.0 mmol) and amine (10.0 mmol) in anhyd DCE (20 mL) was stirred at ambient temperature under an N_2 atm for 45 min. $NaBH(OAc)_3$ (1.5 g, 7.0 mmol) was added in small portions over ca. 30 min and stirring was continued. After 4 h, the reaction mixture was diluted with EtOAc (80 mL), filtered, and washed with 1 N NaOH (25 mL) followed by brine (25 mL). The organic layer was dried over anhyd $MgSO_4$, filtered, and concd. The residue was purified using a general acid–base purification procedure as follows: the crude product was dissolved in EtOAc (50 mL) and the organic layer was extracted with 1.5 N HCl (25 mL). The aq layer was basified to ca. pH 12 with 1 N NaOH and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhyd $MgSO_4$, filtered and concd to afford the desired product (HPLC purity >98%).

Method B: Using Triethylamine and the Reacting Amine

A suspension of aldehyde bisulfite adduct (5.0 mmol) and Et_3N (0.76 g, 5.5 mmol) in anhyd DCE (20 mL) was stirred at ambient temperature under an N_2 atm for 15 min. The amine (5.5 mmol) was added and the reaction mixture was stirred for 45 min following which $NaBH(OAc)_3$ (1.5 g, 7.0 mmol) was added in small portions over ca. 30 min and stirring was continued. After 16 h, the reaction mixture was diluted with EtOAc (80 mL), and washed with 1 N NaOH (25 mL) followed by brine (25 mL). The organic layer was dried over anhyd $MgSO_4$, filtered and concd. The crude material was purified using the general acid–base purification procedure described above.

1-Benzylpiperidine (Table 2, Entry 1b)

Yield: 85%; oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 5 H), 3.49 (s, 2 H), 2.39 (br s, 4 H), 1.60–1.54 (m, 4 H), 1.42 (br s, 2 H).

HRMS (TOF ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}N$: 176.1434; found: 176.1426.

4-Benzylmorpholine (Table 2, Entry 1d)

Yield: 87%; oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.21 (m, 5 H), 3.70 (t, *J* = 4.7 Hz, 4 H), 3.50 (s, 2 H), 2.44 (t, *J* = 4.4 Hz, 4 H).

HRMS (TOF ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}NO$: 178.1226; found: 178.1219.

1-(4-Ethylbenzyl)pyrrolidine (Table 2, Entry 2a)

Yield: 84%; oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 3.59 (s, 2 H), 2.63 (q, *J* = 7.6 Hz, 2 H), 2.55–2.46 (m, 4 H), 1.81–1.74 (m, 4 H), 1.23 (t, *J* = 7.6 Hz, 3 H).

HRMS (TOF ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}N$: 190.1590; found: 190.1590.

1-(4-Methoxybenzyl)pyrrolidine (Table 2, Entry 3a)

Yield: 85%; oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.25 (m, 2 H), 6.88–6.83 (m, 2 H), 3.80 (s, 3 H), 3.62 (br s, 2 H), 2.60–2.54 (m, 4 H), 1.84–1.78 (m, 4 H).

HRMS (TOF ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}NO$: 192.1383; found: 192.1391.

***N*-Ethyl-*N*-(4-methoxybenzyl)ethanamine (Table 2, Entry 3b)**

Yield: 88%; oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2 H), 6.85 (dd, *J* = 8.7, 2.1 Hz, 2 H), 3.78 (s, 3 H), 3.50 (s, 2 H), 2.50 (q, *J* = 7.1 Hz, 4 H), 1.03 (t, *J* = 7.1 Hz, 6 H).

HRMS (TOF ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{20}NO$: 194.1539; found: 194.1531.

1-(3-Phenylpropyl)pyrrolidine (Table 2, Entry 4a)

Yield: 80%; oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2 H), 7.20–7.15 (m, 3 H), 2.65 (t, *J* = 7.7 Hz, 2 H), 2.55–2.43 (m, 6 H), 1.90–1.73 (m, 6 H).

HRMS (TOF ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}N$: 190.1590; found: 190.1581.

4-(3-Phenylpropyl)morpholine (Table 2, Entry 4b)

Yield: 83%; oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2 H), 7.19–7.17 (m, 3 H), 3.71 (t, *J* = 4.6 Hz, 4 H), 2.64 (t, *J* = 7.6 Hz, 2 H), 2.45–2.32 (m, 6 H), 1.87–1.77 (m, 2 H).

HRMS (TOF ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{20}NO$: 206.1539; found: 206.1544.

***N*-Benzyl-1-cyclohexyl-*N*-methylmethanamine (Table 2, Entry 5)**

Yield: 79%; oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 5 H), 3.44 (s, 2 H), 2.15 (s, 3 H), 2.13 (s, 2 H), 1.84–1.80 (m, 2 H), 1.72–1.64 (m, 3 H), 1.54–1.48 (m, 1 H), 1.28–1.12 (m, 3 H), 0.88–0.78 (m, 2 H).

HRMS (TOF ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{24}N$: 218.1903; found: 218.1912.

Sodium 2-Cyclopentyl-1-hydroxyethanesulfonate (2a)

A 500 mL round-bottomed flask was charged with anhyd CH_2Cl_2 (90 mL) and PCC (20.4 g, 94.6 mmol), and the reaction mixture was cooled to 0 °C. A soln of 2-cyclopentylethanol **1** (9.0 g, 78.9 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise over 20 min and the reaction was removed from the cooling bath and stirred at ambient temperature for 2 h. The reaction mixture was diluted with Et_2O (100 mL) with stirring, cooled to 0 °C and decanted. The residue was triturated with Et_2O (3 × 75 mL) followed by decanting. The organic layers were pooled and diluted with EtOH (50 mL). A soln of $NaHSO_3$ (9.0 g, 86.5 mmol) in H_2O (30 mL) was added dropwise over 0.5 h with vigorous stirring and the resulting suspension was stirred at ambient temperature overnight. The reaction mixture was partially concd to remove lower boiling volatiles and the resulting suspension was diluted with EtOH (50 mL) and stirred at 0 °C for 2 h. The precipitate was collected by suction filtration. The filter-cake was washed with hexanes (2 × 50 mL) and dried in vacuo to afford the title compound as a pale-blue powder; yield: 13.7 g (81%). Recrystallization of a small sample from EtOH–H_2O furnished white crystalline plates; mp 168–172 °C (dec.).

^{1}H NMR (500 MHz, D_2O): δ = 4.31 (dd, *J* = 9.2, 3.4 Hz, 1 H), 2.00–1.84 (m, 1 H), 1.80–1.63 (m, 4 H), 1.60–1.37 (m, 4 H), 1.15–0.98 (m, 2 H).

^{13}C NMR (100 MHz, D_2O): δ = 83.8, 37.0, 35.9, 32.8, 31.2, 24.6, 24.5.

HRMS (TOF ESI): *m/z* [M – Na]$^-$ calcd for $C_7H_{13}O_4S$: 193.0540; found: 193.0551.

Anal. Calcd for $C_7H_{13}O_4SNa{\cdot}0.5H_2O$: C, 37.35; H, 6.28; S, 14.25. Found: C, 37.07; H, 6.16; S, 14.43.

***trans*-*N*-(1-Acetyl-2,3-dihydro-1*H*-indol-6-yl)-3-(3-cyanophenyl)-*N*-[1-(2-cyclopentylethyl)piperidin-4-yl]acrylamide (4)**

A 500 mL round-bottomed flask was charged with anhyd DCE (100 mL), sodium 2-cyclopentyl-1-hydroxyethanesulfonate (**2a**) (6.5 g, 30.0 mmol), powdered 4 Å MS (3.0 g) and Et_3N (3.0 g, 30.0 mmol) and the resulting suspension was stirred at ambient temperature for 10 min. *trans*-*N*-(1-acetyl-2,3-dihydro-1*H*-indol-6-yl)-3-(3-cyanophenyl)-*N*-piperidin-4-yl-acrylamide (**3**)[7] (10.3 g, 24.9 mmol) was added in one portion and the reaction mixture was maintained at ambient temperature for 40 min, following which $NaBH(OAc)_3$ (7.4 g, 34.9 mmol) was added in small portions over 0.5 h. The reaction was stirred at ambient temperature overnight. Celite (50.0 g) and EtOAc (200 mL) were added and the reaction was stirred for 10 min and filtered. The filtrate was washed with 0.5 N NaOH (200 mL) and brine (250 mL). The organic layer was dried over anhyd Na_2SO_4, filtered and concd to give a pale-yellow semi-solid. The crude product was purified by silica gel column chromatography (MeOH–CH_2Cl_2, 1%–4%) to afford the title compound as a pale-yellow foam; yield: 9.0 g (71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.59 (d, *J* = 15.5 Hz, 1 H), 7.53–7.49 (m, 3 H), 7.40–7.37 (m, 1 H), 7.20–7.19 (m, 1 H), 6.78–6.73 (m, 1 H), 6.22 (d, *J* = 15.5 Hz, 1 H), 4.72 (br s, 1 H), 4.22–4.11 (m, 2 H), 3.34–3.24 (m, 2 H), 2.96 (br s, 1 H), 2.30–2.24 (m, 5 H), 2.08–1.86 (m, 6 H), 1.71–1.44 (m, 10 H), 1.07–1.03 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 164.8, 144.0, 138.8, 137.1, 136.7, 132.8, 132.1, 131.7, 130.2, 129.4, 125.6, 124.8, 122.2, 118.9, 118.5, 112.7, 77.3, 76.7, 57.8, 53.1, 52.9, 49.2, 45.9, 38.3, 33.3, 32.6, 30.2, 27.7, 25.0, 24.1, 9.5.

HRMS (TOF ESI): *m/z* [M + H]$^+$ calcd for $C_{32}H_{39}N_4O_2$: 511.2995; found: 511.2921.

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References

(1) Ehrlich, J.; Bogart, M. T. *J. Org. Chem.* **1947**, *12*, 522.
(2) (a) Cymerman Craig, J.; Hamon, D. P. G. *J. Org. Chem.* **1965**, *30*, 4168. (b) Kimura, M.; Seki, M. *Tetrahedron Lett.* **2004**, *45*, 3219. (c) Bio, M. M.; Hansen, K. B.; Gipson, J. *Org. Process Res. Dev.* **2008**, *12*, 892.
(3) Kjell, P. D.; Slattery, B. J.; Semo, M. J. *J. Org. Chem.* **1999**, *64*, 5722.
(4) Baxter, E. W.; Reitz, A. B. In *Organic Reactions*, Vol. 59; Overman, L. E., Ed.; John Wiley & Sons: New York, **2002**, 1–714.
(5) Ragan, J. A.; am Ende, D. J.; Brenek, S. J.; Eisenbeis, S. A.; Singer, R. A.; Tickner, D. L.; Teixeira, J. J. Jr.; Vanderplas, B. C.; Weston, N. *Org. Process Res. Dev.* **2003**, *7*, 155.
(6) Bonaventure, P.; Nepomuceno, D.; Mazur, C.; Lord, B.; Rudolph, D. A.; Jablonowski, J. A.; Carruthers, N. I.; Lovenberg, T. W. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 1130.
(7) Jablonowski, J. A.; Chai, W.; Li, X.; Rudolph, D. A.; Murray, W. V.; Youngman, M. A.; Dax, S. L.; Nepomuceno, D.; Bonaventure, P.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1239.
(8) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2253.
(9) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.