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Direct Reductive Amination of Aldehyde Bisulfite Adducts Induced by 2-Picoline Borane: Application to the Synthesis of a DPP-IV Inhibitor

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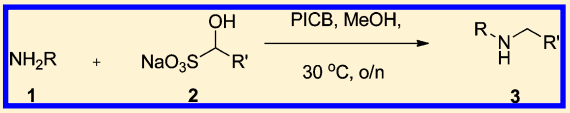
Supporting Information

ABSTRACT: Aldehyde-bisulfite adducts dervied from unstable parent aldehydes were reductively alkylated in a direct fashion with a variety of amines. This approach features the use of 2-picoline borane as the reducing agent and a protic solvent for the reaction media and has been successfully applied to the synthesis of a DPP-IV inhibitor and a variety of other amines.



Bisulfite adducts are known to confer chemical stability to the parent aldehyde and exhibit desirable physical properties such as crystallinity, facilitating their use as isolation and purification techniques.[1] Subsequent use of the bisulfite adduct often requires treatment with aqueous conditions to reveal the aldehyde functionality followed by extraction into an organic solvent for further utilization.[2−4] There are few reported uses of directly engaging bisulfite adducts in synthetic transformations without the need for regeneration of the aldehyde prior to use.[5−8] Herein we report that a variety of aldehyde bisulfite adducts derived from unstable parent aldehydes were reductively alkylated with amines by 2-picoline borane as the reducing agent. In addition to providing direct access to derivatives, the bisulfite adduct preparation provides characterizable bench-stable solids, which is especially important for those aldehydes that are unstable or prone to side reactions.

Recently we had the need to develop the reductive amination of **4** with **5** to give DPP-IV inhibitor (**6**) (Scheme 1), which is an investigational candidate for the treatment of type II diabetes mellitus. A number of significant issues were identified with the cyanopyrrolidine hemiacetal (**5**) that precluded its long-term use for this transformation. Cyanopyrrolidine hemiacetal (**5**) has stability issues[9] and requires cryogenic storage precautions and furthermore is a highly water-soluble liquid (>300 mg/g), which causes complications during workup and isolation procedures. It was envisioned that the bisulfite adduct of **5** could provide the solution to these challenges.

Application of the sodium bisulfite reactive crystallization method, which involves treating an alcoholic solution of the aldehyde with aqueous $NaHSO_3$ at elevated temperatures, was successfully applied to the isolation of the bench stable aldehyde bisulfite adduct **2a**. Since we were interested in exploring the scope of the direct reductive amination, we prepared a variety of bisulfite adduct substrates using this approach. The substrate selection process was predicated on the inherent instability of the parent aldehyde. The majority of the aldehydes selected have been reported to exhibit sensitivities to moisture, light, and oxygen, have been observed to readily polymerize and decompose on storage,[10] or are volatile and not easy to handle. Formation of the corresponding bisulfite adducts proceeded in good yields while also conferring the desired stability[11] to the substrate **2a−2e** (Table 1).

We were encouraged by literature examples reporting the use of bisulfite adducts in reductive aminations. Ragan and coworkers have reported the direct reductive amination of an amine salt with an aldehyde bisulfite adduct, which proceeds *via* an iminium intermediate that is subsequently reduced using $NaBH(OAc)_3$.[5] Limitations with this approach do however exist, including the azeotropic removal of water at elevated temperatures (105 °C), use of NMP/cyclohexane cosolvent, as well as the modest 55% yield reported. Recently, secondary amines were reductively alkylated directly with aldehyde-bisulfite adducts using $NaBH(OAc)_3$ in 1,2-DCE in the presence of molecular sieves.[6] This method, however, was limited to secondary amines, which have a reduced risk of byproduct potential, and furthermore, the approach encompassed otherwise stable parent aldehydes. As such, further exploration of this reaction protocol with an emphasis on utilizing unstable aldehyde precursors as well as expanding the scope of the amine substrate is warranted.

An extensive solvent and base screen was conducted to identify the optimium conditions for the bisulfite adduct salt break[2] and reductive amination.[13] To our delight, two promising conditions were identified: Et_3N (83%) and NaOAc (87%) in MeOH. In the case of Et_3N as the base in DCM, 13% of a byproduct was obtained and identified as the cyclization side product (**8**).[14] Use of MeOH as the solvent minimized the side product formation to <3% with Et_3N and to <1.5% with NaOAc.[15] On the basis of the screening results, NaOAc was the most attractive base, giving the product in good assay yield, reaction conversion, and purity profile, and as such was pursued for further development.

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Scheme 1. Initial Conditions for Preparation of DPP-IV Inhibitor (6)

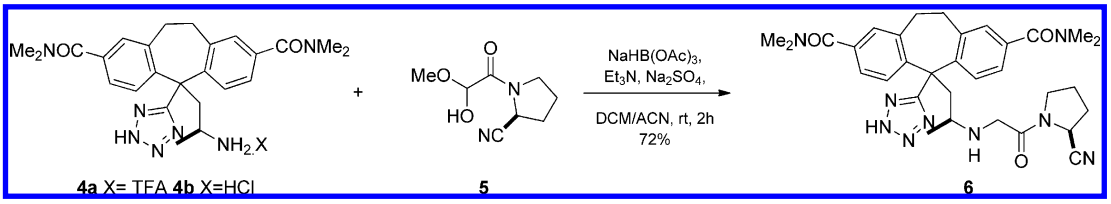
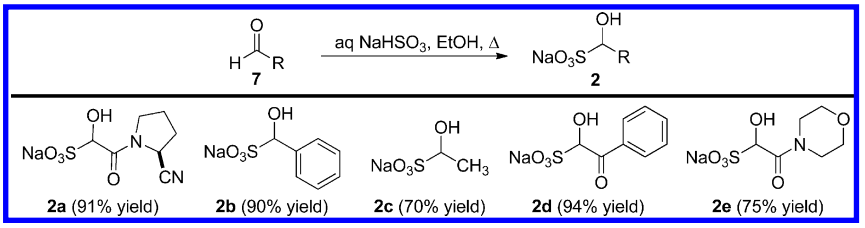


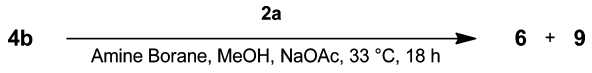
Table 1. Preparation of Bisulfite Adduct *via* Reactive Crystallization Method[12]



Having identified a suitable solvent and base combination, we turned our attention to the hydride source. $NaBH(OAc)_3$ is a commonly used hydride source in reductive aminations; however, reproducibility issues were being encountered during development work and attributed to stability issues that can arise when using $NaBH(OAc)_3$ in protic solvents.[16] As such, we sought to identify an alternative hydride source that is more compatible with the prescribed conditions.

Amine borane complexes were viewed as viable alternatives to $NaBH(OAc)_3$ for reductive aminations run in MeOH.[17−22] A number of amine boranes were screened in the direct reductive amination including 2-picoline borane (PICB),[23−25] triethylamine borane, pyridine borane, and diethylphenylamine borane (Table 2). As can be seen from Table 2, triethylamine

Table 2. Amine Borane Screen



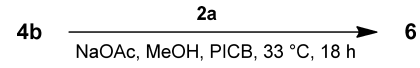
entry[a]	amine borane	9 (%)[b]	product assay yield (%)[c]
1	triethylamine borane	3.8	46
2	pyridine borane	11	77
3	2-picoline borane	5.5	84
4	diethylphenylamine borane	0.3	64

[a]Reactions conducted on 0.1 mmol scale with **2a** (2 equiv), amine borane (1.0 equiv), and NaOAc (3 equiv). [b]Determined on crude reaction mixture by HPLC analysis. [c]Weight % yield determined by quantitative HPLC analysis.

borane (entry 1) gave the product in a low assay yield of 46% with 31% unreacted starting material (**4b**). Pyridine borane (entry 2) resulted in an improved yield; however, unlike $NaBH(OAc)_3$ use of pyridine borane[26] did result in 11% of the overalkyation side product (**9**).[27] Diethylphenylamine borane gave the product in a modest assay yield of 64% with 32% unreacted starting material (**4b**) observed (entry 4). Use of PICB gave the product in the highest assay yield of 88% with only 5.5% of **9** observed (entry 3). As such, PICB was selected for further development since it offers a number of advantages, most notably its tolerance to protic environments, the availability of 3 hydrides per equilvalent of reagent, as well as improved shelf life and thermal stability (thermally stable up to 100 °C).

A small screen was conducted to determine the optimal equivalents for the bisulfite adduct and PICB reagent (Table 3).

Table 3. Optimization of PICB and Bisulfite Adduct Equivalents



entry[a]	2a	PICB equiv	8 (%)[b]	9 (%)[b]	product assay yield (%)[c]
1	1.3	1	1.2	5.1	85
2	1.3	0.6	1	3.3	88
3	1.5	1	1.2	6.6	81
4	1.5	0.6	0.6	3.8	88

[a]Reactions conducted on 0.1 mmol scale with NaOAc (3 equiv). [b]Determined on crude reaction mixture by HPLC analysis. [c]Weight % yield determined by quantitative HPLC analysis.

Use of 1.3 equiv of bisulfite adduct with 1 equiv of PICB gave the product in an 85% assay yield with 5.1% of overalkyated side product (**9**) (entry 1). Lowering the equivalents of PICB to 0.6 did not adversely affect the reaction conversion and resulted in a slight reduction of the overalkyation side product (**9**) (entry 2). Increasing the bisulfite adduct equivalents to 1.5 in combination with 1 equiv of PICB results in a reduction in the assay yield of product and an increase in **9** (entry 3). Lowering the PICB equivalents to 0.6 gave comparable results to entry 2, albeit with a slight increase in the level of overalkylation side product **9**. As such, we advanced forward with 1.3 equiv of bisulfite adduct and 0.6 equiv of PICB. With the optimal reaction conditions identified, the reductive amination was demonstrated successfully on gram scale by treatment of amine salt (**4b**) with bisulfite adduct (**2a**) (1.3 equiv), NaOAc (3.0 equiv), and PICB (0.6 equiv) in MeOH at 33 °C for 4 h. The product (**6**) was isolated directly from the reaction mixture in 84% isolated yield and gratifyingly provided a higher yield than the original conditions described earlier whereby the cyanopyrrolidine hemiacetal (**5**) was employed (72% isolated yield).

As mentioned previously, we were interested in exploring the generality and scope of the direct reductive aminiation. Our investigations began by examining the reductive amination of benzaldehyde bisulfite adduct (**2b**) and aniline (**1a**) as a prototypical reaction (Table 4). Using the previously mentioned conditions (NaOAc, PICB, MeOH) the reaction

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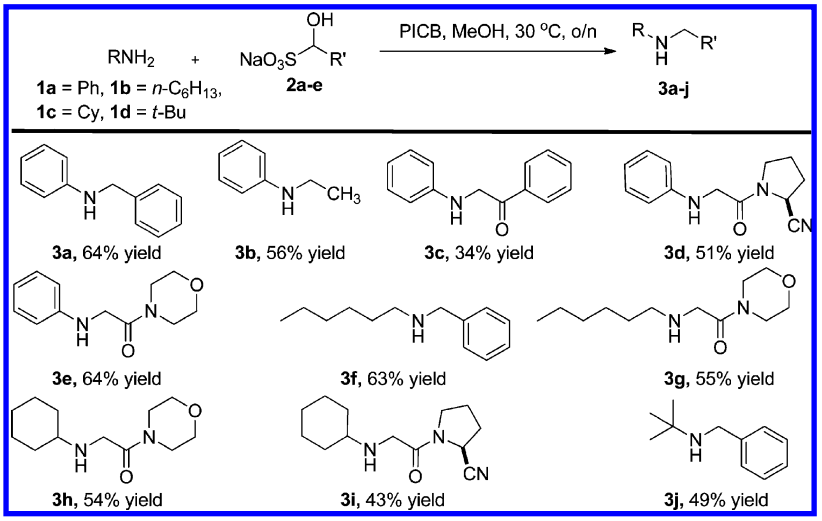
Table 4. Direct Reductive Amination of Various Amines with Bisulfite Adduct Substrates



took place to give **3a** in 51% yield with 15% overalkylation side product.[28,29] In order to suppress overalkyation, we investigated the use of excess starting amine (2 equiv), which would serve the dual purpose of facilitating the salt break as well as participating as the amine substrate.[6] In the event, we were pleased to see an improvement in the product distribution and enhancement in assay yield of 69% (**3a**) with <2% overalkyation side product [(64% isolated yield) Table 4]. The developed reaction protocol was applied and shown to work effectively with a variety of amine and bisulfite adduct substrates giving clean reaction profiles in moderate to good yields.[30]

In summary, we have developed an efficient and general reaction protocol for the direct reductive amination of bisulfite adducts with amines using 2-picoline borane in a protic solvent. The conditions were designed to simultenously demonstrate the utility of bisulfite adducts in providing enhanced chemical stability to the parent aldehyde while maintaining the required level of reactivity for coupling with a broad range of amine substrates. The mild reaction conditions are effective in attenuating the side product distribution and can be adapted for use with either excess amine substrate or an exogenous base and do not require water remediation procedures.

■ EXPERIMENTAL SECTION

The identity of known compounds was confirmed by ^{1}H and ^{13}C NMR after comparison with previously reported data: sodium hydroxy(phenyl)methanesulfonate (**2b**),[31] *N*-benzylaniline (**3a**)[32] [purification by silica gel chromotography (10% EtOAc/heptane)], *N*-ethylaniline (**3b**)[33] [purification by silica gel chromotography (10% EtOAc/heptane)], 1-phenyl-2-(phenylamino)ethanone (**3c**)[34] [purification by silica gel chromotography (10% EtOAc/heptane)], *N*-benzylhexan-1-amine (**3f**)[35] [purification by silica gel chromotography (30% EtOAc/heptane)], (*S*)-1-(2-(cyclohexylamino)acetyl)-pyrrolidine-2-carbonitrile (**3i**)[36] [purification by silica gel chromotography (10% 2 M NH_3 in MeOH/DCM)], and *N*-benzyl-2-methylpropan-2-amine (**3j**)[37] [purification by silica gel chromotography (30% EtOAc/heptane)].

General Procedure for the Formation of Aldehyde Bisulfite Adducts. To a round-bottom flask equipped with a magnetic stir bar and under an atmosphere of N_2 was charged aldehyde (33 mmol) followed by EtOH (50 mL). To the reaction mixture was charged a solution of $Na_2S_2O_5$ (23 mmol) in H_2O (5 mL), and the reaction mixture was subsequently heated until complete consumption of starting aldehyde was observed. The heterogeneous reaction mixture was cooled to ambient temperature, stirred for 4 h, and then isolated by vacuum filtration. The product cake was washed with EtOH (3 × 2 mL) and subsequently dried under vacuum.

General Procedure for Direct Reductive Amination. To a 20-mL reaction vial equipped with a magnetic stir bar was charged aldehyde bisulfite adduct (2.0 mmol), 2-picoline borane (2.0 mmol), MeOH (5 mL), and amine (4.0 mmol). The reaction mixture was warmed to 30 °C and stirred for 18 h. The precipitated solids were filtered off by vacuum filtration, and the filtrate was reduced *in vacuo*, then treated with 2 N HCl (10 mL), and subsequently stirred for 30 min. The reaction mixture was cooled to 0 °C, and aqueous Na_2CO_3 was slowly added to neutralize the solution. The reaction mixture was then extracted with MTBE (3 × 25 mL), dried over anhydrous $MgSO_4$, and reduced *in vacuo* to afford the crude product. Further purification of the product was achieved by silica gel chromatography.

Known Compounds for Which No Previously Reported NMR Spectral Data Is Available. *Sodium 1-Hydroxyethanesulfonate (**2c**).* White crystalline solid (8.9 g, 70% yield); thermal decomposition of the compound prohibits melting point measurement. ^{1}H NMR (400 MHz, D_2O): δ 1.49 (d, J = 6.65 Hz, 3H), 4.58 (q, J = 6.46 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O): δ 16.9, 80.4.

*Sodium 1-Hydroxy-2-oxo-2-phenylethanesulfonate (**2d**).* White crystalline solid (735 mg, 94% yield); thermal decomposition of the compound prohibits melting point measurement. ^{1}H NMR (400 MHz, D_2O): δ 6.19 (s, 1H), 7.53−7.57 (m, 2H), 7.69−7.73 (m, 1H), 8.02−8.04 (m, 2H). ^{13}C NMR (100 MHz, D_2O): δ 84.2, 128.7, 129.4, 134.6, 134.8, 196.3. HRMS (ESI-Orbitrap) calcd for $C_8H_7NaO_5S$: [M + Na] m/z 260.9810, found 260.9800.

*1-Morpholino-2-(phenylamino)ethanone (**3e**).* Purification by silica gel chromotography (70% EtOAc/Heptane) gave the product as an off-white crystalline solid (252 mg, 64% yield); mp 110−112 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.40−3.50 (m, 2H), 3.65−3.75 (m, 6H), 3.86 (s, 2H), 4.7 (br s, 1H), 6.62−6.64 (m, 2H), 6.71−6.75 (m, 1H), 7.17−7.21 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 42.3, 44.7, 45.2, 66.4, 66.8, 113.0, 117.7, 129.3, 147.3, 167.8. HRMS (ESI-Orbitrap) calcd for $C_{12}H_{16}N_2O_2$: [M + H] m/z 221.1290, found 221.1279.

Analytical Data for New Compounds. *5H-Dibenzo[a,d]-cycloheptene-2,8-dicarboxamide, 5-[(2S)-2-[[2-[(2S)-2-Cyano-1-pyrrolidinyl]-2-oxoethyl]amino]propyl]-10,11-dihydro-N^2,N^2,N^8,N^8-tetramethyl-5-2H-tetrazol-5-yl·Pentahydrate (**6**).* Compound **4b** (1000 mg, 2.0 mmol) was dissolved in MeOH (5 mL), and sodium acetate (445 mg, 5.4 mmol), bisulfite adduct **2a** (647 mg, 2.5 mmol), and 2-picoline borane (122 mg, 1.15 mmol) were charged sequentially to the reaction mixture and heated to 30 °C for 4 h. Water (1.5 mL) was charged to the reaction mixture, and the resulting suspension was heated to 45 °C for 1 h, cooled to room temperature, and filtered through a sintered glass filter funnel to give a white crystalline solid

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(1.23 g, 84% yield); thermal decomposition of the compound prohibits melting point measurement. $[\alpha]_D$ −21 (*c* 0.01, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.8 (d, *J* = 6.7 Hz, 3H), 1.9−2.1 (m, 2H), 2.1−2.3 (m, 2H), 2.5−2.6 (d, *J* = 14.9 Hz, 1H), 2.7−2.8 (m, 1H), 2.8−3.0 (s+m, 14H), 3.0−3.5 (m, 6H), 3.9 (d, *J* = 16.5 Hz, 1H), 4.1 (d, *J* = 16.5 Hz, 1H), 4.9−5.1 (m, 1H), 6.1 (d, *J* = 8.0 Hz, 1H), 6.5 (d, *J* = 8.3 Hz, 1H), 6.9−7.0 (d, *J* = 9.2 Hz, 1H), 7.0−7.1 (d, *J* = 9.0 Hz, 1H), 7.1 (s, 1H), 7.3 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 18.5, 24.6, 29.7, 34.5, 34.7, 35.9, 44.4, 45.4, 46.3, 49.9, 54.8, 119.0, 123.9, 124.1, 127.9, 129.3, 131.3, 131.8, 133.9, 135.1, 139.1, 142.2, 142.5, 145.6, 165.5, 168.0, 169.7, 172.0. HRMS (ESI-Orbitrap) calcd for $C_{32}H_{39}N_9O_3$: [M + H] *m*/*z* 598.3254, found 598.3246.

*Sodium 2-((S)-2-Cyanopyrrolidin-1-yl)-1-hydroxy-2-oxoethanesulfonate (**2a**).* White crystalline solid (26.96 g, 91% yield); thermal decomposition of the compound prohibits melting point measurement. ^{1}H NMR (400 MHz, D_2O): diastereomeric mixture (∼1:1) δ 2.05−2.16 (m, 4H), 2.27−2.33 (m, 4H), 3.65−3.71 (m, 1H), 3.80−3.83 (m, 1H), 4.74−4.77 (m, 1H), 4.80−4.82 (m, 1H), 5.27 (s, 1H), 5.29 (s, 1H). ^{13}C NMR (100 MHz, D_2O): 24.6, 24.8, 29.3, 29.5, 47.3, 47.6, 47.7, 47.8, 81.2, 81.2, 118.7, 118.9, 167.1, 166.9. HRMS (ESI-Orbitrap) calcd for $C_7H_9N_2NaO_5S$: [M + Na] *m*/*z* 279.0028, found 279.0017.

*Sodium 1-Hydroxy-2-morpholino-2-oxoethanesulfonate (**2e**).* White crystalline solid (2.2 g, 75% yield); thermal decomposition of the compound prohibits melting point measurement. ^{1}H NMR (400 MHz, D_2O): δ 3.55−3.81 (m, 4H), 5.50 (s, 1H). ^{13}C NMR (100 MHz, D_2O): δ 43.2, 46.8, 66.1, 79.4, 166.3. HRMS (ESI-Orbitrap) calcd for $C_6H_{10}NNaO_6S$: [M + Na] *m*/*z* 270.0024, found 270.0013.

*(S)-1-(2-(Phenylamino)acetyl)pyrrolidine-2-carbonitrile (**3d**).* Purification by silica gel chromotography (70% EtOAc/Heptane) gave the product as a tan crystalline solid (108 mg, 51% yield); mp 105−107 °C. $[\alpha]_D$ −25.74 (*c* 0.035, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16−2.31 (m, 4H), 3.43−3.45 (m, 1H), 3.59−3.62 (m, 1H), 3.84 (s, 2H), 4.76−4.79 (dd, *J* = 7.24, 3.72 Hz, 1H), 6.61−6.63 (m, 2H), 6.72−6.76 (m, 1H), 7.17−7.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 29.8, 45.3, 46.2, 46.5, 113.0, 117.9, 118.0, 129.2, 146.9, 168.4. HRMS (ESI-Orbitrap) calcd for $C_{13}H_{15}N_3O$: [M + H] *m*/*z* 230.1293, found 230.1282.

*2-(Hexylamino)-1-morpholinoethanone (**3g**).* Purification by silica gel chromotography (70% EtOAc/Heptane) gave the product as a clear colorless oil (170 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.50 Hz, 3H), 1.21−1.41 (m, 6H), 1.52 (quin, *J* = 7.40 Hz, 2H), 1.86 (s, 1H), 2.59 (t, *J* = 7.24 Hz, 2H), 3.41 (s, 4H), 3.58−3.73 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 27.0, 30.2, 31.8, 42.1, 45.0, 50.3, 50.6, 66.6, 66.9, 169.9. HRMS (ESI-Orbitrap) calcd for $C_{12}H_{24}N_2O_2$: [M + H] *m*/*z* 229.1916, found 229.1903.

*2-(Cyclohexylamino)-1-morpholinoethanone (**3h**).* Purification by silica gel chromotography (10% MeOH/DCM) gave the product as a clear colorless oil (223 mg, 54% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93−1.07 (m, 2H), 1.08−1.28 (m,3 H), 1.46−1.58 (m, 1H), 1.60−1.71 (m, 2H), 1.73−1.86 (m, 2H), 2.29 (tt *J*=9.78, 3.52 Hz, 1H), 3.30 (br s, 1H), 3.36 (s, 2H), 3.38−3.47 (m, 4H), 3.51−3.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 26.0, 33.4, 42.1, 44.9, 47.7, 56.9, 66.5, 66.8, 170.0. HRMS (ESI-Orbitrap) calcd for $C_{12}H_{22}N_2O_2$: [M + H] *m*/*z* 227.1760, found 227.1748.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data for all new compounds is available free of charge *via* Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Oil that must be stored in solution, shown to have poor stability above −20 °C.

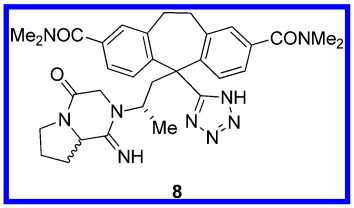
(10) For the synthesis and reported instability of the morpholino phenyl glyoxal substrate, see: Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066−14067.

(11) Bisulfite adducts **2a**−**2e** have been observed to be bench stable for at least 12 months.

(12) Yield based upon quantitative ^{1}H NMR of the substrate against an external standard.

(13) See Supporting Information for details regarding base screen.

(14) The cyclization side product arises as a result of an intramolecular reaction of the free amine and proline nitrile.



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(15) It should be noted that conducting the reaction in MeOH results in precipitation of the product from the reaction mixture, which is believed to be primarily responsible for reduced levels of the side product.

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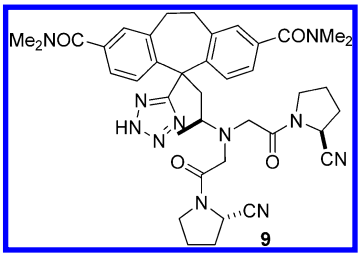
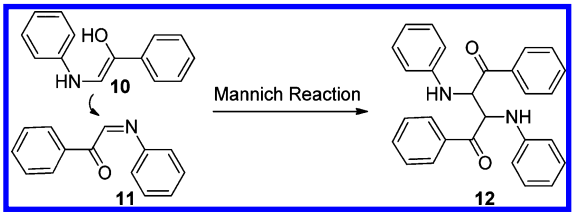
(26) Pyridine borane decomposes at temperatures >54 °C, which precluded further optimization of this reagent. Amine Borane; Callery Chemical Technical Bulletin, 2002, p 9.
(27) Overalylation side product:



(28) Product distribution determined by HPLC analysis of the crude reaction mixture.
(29) Overalkylation side product proposed based on LCMS analysis data.
(30) In the case of the phenyl glyoxal derived bisulfite adduct, the low yield was attributed to the formation of an interesting side product, which was isolated and identified as dimer **12**. Formation of this side product is believed to arise as a result of **10** reacting with **11** *via* a Mannich reaction.



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