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Synthesis of non-symmetrical 3,5-diamidobenzyl amines, ethers and sulfides

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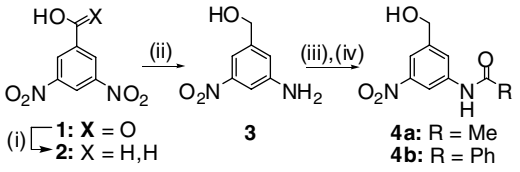
Abstract

A straightforward synthesis of non-symmetrical 3,5-diamidobenzyl amines, ethers and sulfides starting from 3,5-dinitrobenzoic acid is reported. Functionalization of the benzylic position is only achieved after formation of the two amides, otherwise benzylic hydrogenolysis occurs during nitro group reduction.

meta-Diamidobenzenes are a moiety found in many compound classes including polybenzamide DNA minor-groove binding agents and benzamide polymers.[1–5] We wished to synthesize and incorporate non-symmetrical 3,5-diamidobenzylamines into polybenzamide DNA minor-groove binding agents with the aim of testing what effect the additional polar amine moieties would have on DNA binding. Whilst there are numerous examples of symmetrical 3,5-diamidobenzenes, generally formed from the diacylation of 3,5-diaminobenzenes, we were surprised to find a lack of information on these deceptively simple, substituted benzene derivatives. Herein, we report the synthesis of a range of non-symmetrical 3,5-diamidobenzyl amines, ethers and sulfides.

Starting from the commercially available 3,5-dinitrobenzyl alcohol **2**, which can also conveniently be obtained on a large scale from the borane reduction of 3,5-dinitrobenzoic acid **1**,[6] selective reduction of one nitro group using aqueous ammonium sulfide[7] gave amino alcohol **3** (Scheme 1). It should be noted that attempts to selectively mono reduce *N*,*N*-diethyl-3,5-nitrobenzylamine[8] using the same conditions led to the formation of a complex mixture of products. Attempts to selectively acylate the amino group of **3** with 1 equiv of either acetic anhydride or benzoyl chloride gave a mixture of N-, O- and diacylated products. This problem was circumvented by reacting **3** with either an excess of acetic anhydride or benzoyl chloride to give the diacylated product, followed by selective hydrolysis of the ester using aqueous sodium hydroxide to give acetamide alcohol **4a**[9,10] in 90% yield or benzamide alcohol **4b** in 95% yield, respectively, over two steps.



Scheme 1. Reagents, conditions and yields: (i) BH_3–THF, THF, 0 °C to rt, 18 h, 78%; (ii) 20% aq $(NH_4)_2S$, MeOH, reflux, 6 h, then rt 20 h, 86%; (iii) for **4a**, 3 equiv Ac_2O, NEt_3, DMF, rt, 24 h, 92%, for **4b**, 3 equiv BzCl, NEt_3, DCM, rt 3 h, 99%; (iv) 2 equiv NaOH, 4:1 EtOH/H_2O, rt, 3 h, **4a** 98%, **4b** 96%.

Next, we planned to convert the benzylic alcohols into the desired benzylic amines before reducing the second aromatic nitro group. Attempts to couple alcohol **4b** with various secondary amines under Mitsunobu conditions failed, presumably due to the lack of a deprotonatable functionality *ortho* to the benzylic position.[11] Conversion of the benzylic alcohol into a more activated leaving group

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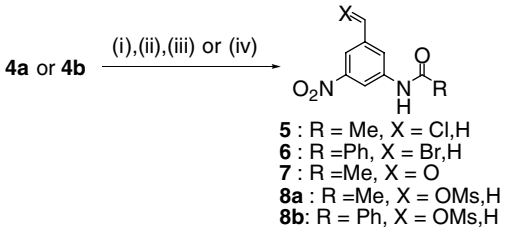
was therefore required. The initial approach was to convert alcohol **4** into chloride **5**. This was achieved using thionyl chloride in DCM to give chloride **5** in 86% yield. However, chloride **5** was found to decompose quickly even when stored at <0 °C and is only useful if used immediately.



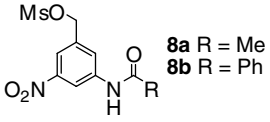
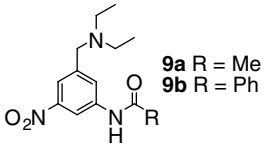
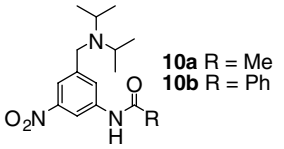
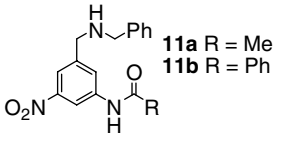
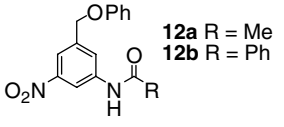
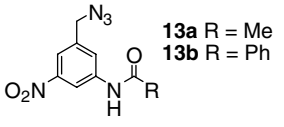
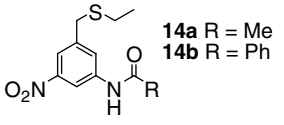
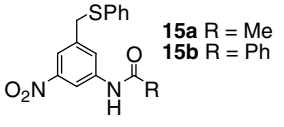
Scheme 2. Reagents, conditions and yields: (i) $SOCl_2$, DCM, rt, 3 h, **5** 86%; (ii) CBr_4, PPh_3, DCM, rt, 24 h, **6** 70%; (iii) MnO_2, DCM, reflux 8 h, then rt 5 days, **7** 26%; (iv) 1.05 equiv MsCl, NEt_3, THF, 0 °C to rt, 6 h, **8a** and **8b** 100%.

We therefore sought a more stable coupling partner; bromide **6** was synthesized in 70% yield using Appel conditions[12] but was found to be as unstable as chloride **5**, whilst aldehyde **7**, which could be converted to the desired amines using reductive amination, was synthesized via a MnO_2 oxidation but in a poor 26% yield. We eventually discovered that benzylic mesylates **8a/b**, which can be synthesized easily in near quantitative yield, had sufficient reactivity and, when stored at <0 °C, are stable for periods over many months (Scheme 2).

With mesylates **8a/b** in hand, we investigated their reactivity with a range of nucleophiles, including amines, thiols, sodium azide and sodium phenolate. The yields were reasonable to excellent for all the nucleophiles examined (Table 1).

With the benzylic position now substituted as desired, the next step was to reduce the remaining nitro group. Unfortunately for tertiary amines **9a/b**, **10a/b**, **11a/b** and

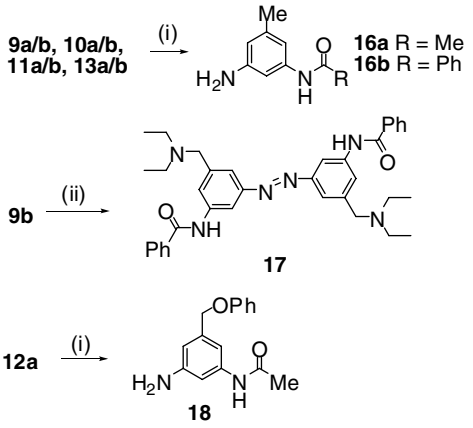
Table 1
Reaction of various nucleophiles with mesylates **8a/b**

Entry	Mesylate	Nucleophile, conditions	Product	Yield[a] (%)
1	 **8a** R = Me **8b** R = Ph	$HNEt_2$, THF, 0 °C to rt, 16 h	 **9a** R = Me **9b** R = Ph	**9a** 72 **9b** 81
2	**8a/b**	HN^iPr_2, THF, 0 °C to rt, 10 h	 **10a** R = Me **10b** R = Ph	**10a** 60 **10b** 70
3	**8a/b**	$PhCH_2NH_2$, THF, reflux, 18 h	 **11a** R = Me **11b** R = Ph	**11a** 92 **11b** 95
4	**8a/b**	PhONa, DMF, rt, 16 h	 **12a** R = Me **12b** R = Ph	**12a** 42 **12b** 65
5	**8a/b**	NaN_3, DMF, 105 °C, 16 h	 **13a** R = Me **13b** R = Ph	**13a** 82 **13b** 79
6	**8a/b**	EtSNa, THF, rt, 24 h	 **14a** R = Me **14b** R = Ph	**14a** 91 **14b** 85
7	**8a/b**	PhSNa, DMF, reflux, 1 h	 **15a** R = Me **15b** R = Ph	**15a** 45 **15b** 70

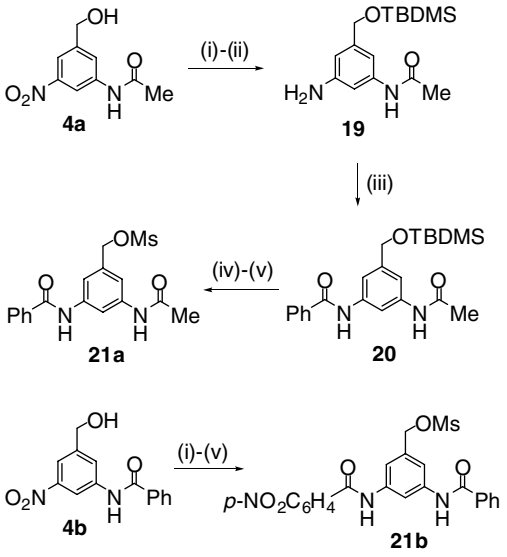
[a] Isolated yield.

azide **13a/b**, under standard hydrogenation conditions, using 10% Pd/C, rapid benzylic hydrogenolysis occurred giving in all cases the 3-amido-5-aminotoluene **16a/b** in near quantitative yield (Scheme 3). Altering the pH to produce either acidic or basic conditions, or using a less active palladium source did not alter the outcome.[13–15] We then turned to metal-based reductions that had previously been reported to work successfully on aromatic nitro compounds bearing a *meta* benzylic amine or ether. However, reductions with $SnCl_2$,[16] Al–$NiCl_2$[17] and $NaBH_4$–$NiCl_2$[18] resulted in either no reaction or total decomposition whilst the use of zinc powder in acetic acid[19] on amine **9b** resulted in a complex mixture with brightly coloured azo-dimer **17** being the predominant (~80%) product. Whilst there are reports of other benzylic amines with a *meta* nitro group that have been successfully reduced,[16,18,20–22] none have an additional *meta* amide functionality. It appears that this additional group subtly alters the reactivity of these molecules such that benzylic cleavage is highly favoured. Investigating the hydrogenation of sulfides **14a/b** and **15a/b** resulted in the formation of a complex mixture of products; however, ^{1}H NMR analysis of the crude mixture showed that toluenes **16a/b** were also present in the mixtures. Hydrogenation of ether **12a**, however, proceeded cleanly to give aniline **18** in quantitative yield.

Since the desired benzylic amines **1** could not be obtained using the method outlined above but ether **12a** could be reduced without benzylic cleavage, we turned to the idea that benzylic alcohols **4a/b** could be protected as an ether, the nitro group reduced and converted into the desired second amido functionality before deprotection of the ether and then conversion into the desired benzylic amines via the mesylate. To test the viability of this reaction sequence, alcohol **4a** was protected using *tert*-butyldimethylsilyl chloride to give the silyl ether, which was then followed by hydrogenation under standard conditions to give aniline **19** in 93% yield over two steps, with no sign of benzylic hydrogenolysis (Scheme 4). Acylation of **19** with benzoyl chloride in pyridine gave bis-amide **20** in



Scheme 3. Reagents, conditions and yields: (i) H_2, 10% Pd/C, MeOH, 2–3 h, >95% in all cases; (ii) Zn powder, AcOH, reflux, 24 h, ~80%.



Scheme 4. Reagents and conditions: (i) TBDMSCl, imidazole, DMF, rt, 2 h, 93%; (ii) H_2, 10% Pd/C, MeOH, 3 h, 100%; (iii) benzoyl chloride (4-nitrobenzoyl chloride for **21b**), pyridine, rt, 16 h, 80%; (iv) 4 equiv TBAF, 4 equiv AcOH, THF, rt, 36 h, 81%; (v) 1.05 equiv MsCl, NEt_3, THF, 100%.

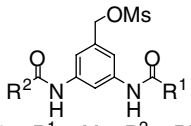
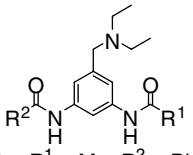
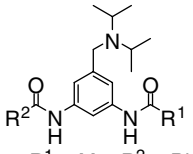
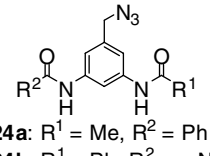
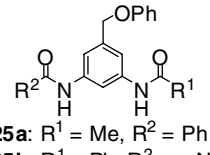
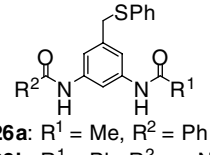
80% yield. Deprotection of the silyl ether with TBAF was greatly improved by using 4 equiv of acetic acid to buffer the pH[23] giving a benzylic alcohol, which underwent mesylation using the previously determined conditions to give mesylate **21a** in 81% yield over two steps.[24] Using the same reaction sequence, alcohol **4b** was converted to bis-amide mesylate **21b** in 57% yield over five steps, the only difference being the use of 4-nitrobenzoyl chloride rather than benzoyl chloride so as to again have differently substituted amides.

We then investigated the ability of these bis-amide mesylates **21a/b** to undergo substitution reactions with a range of nucleophiles.[25] The yields were comparable to those previously obtained when using mesylates **8a/b** except for sulfides **26a/b**, which were isolated in significantly lower yields (Table 2).

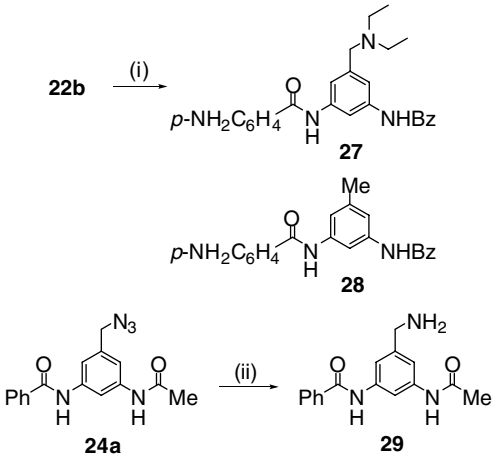
Finally, we wished to determine whether the bis-amide benzylic amines **22a/b**, **23a/b** and azide **24a/b** were as susceptible to hydrogenolysis as mono-amides **9a/b**, **10a/b**, **11a/b**. We were pleased to find that hydrogenation of nitrobenzamide **22b** under standard conditions for 2 h gave an 85% yield of amine **27** (Scheme 5). On repeating the reaction for 24 h, ^{1}H NMR analysis of the crude reaction mixture showed that benzylic cleavage was eventually occurring with ~15% of toluene **28** being produced; however, even after three days complete conversion into toluene **28** had not occurred. Hydrogenation of azide **24a** for 1 h also went smoothly giving a 95% yield of benzylamine **29**.[26]

In summary, we have synthesized non-symmetrical 3,5-diamidobenzyl amines, ethers and sulfides starting from the readily available 3,5-dinitrobenzyl alcohol. Investigations into the role of the 3- and 5-substituent on the rate

Table 2
Reaction of various nucleophiles with mesylates **21a/b**

Entry	Mesylate	Nucleophile, conditions	Product	Yield[a] (%)
1	 **21a**: R^1 = Me, R^2 = Ph **21b**: R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$	$HNEt_2$, THF, rt, 24 h	 **22a**: R^1 = Me, R^2 = Ph **22b**: R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$	**22a** 95 **22b** 89
2	**21a/b**	HN^iPr_2, THF, rt, 10 h	 **23a**: R^1 = Me, R^2 = Ph **23b**: R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$	**23a** 68 **23b** 59
3	**21a/b**	NaN_3, DMF, 105 °C, 24 h	 **24a**: R^1 = Me, R^2 = Ph **24b**: R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$	**24a** 77 **24b** 84
4	**21a/b**	PhONa, DMF, rt, 12 h	 **25a**: R^1 = Me, R^2 = Ph **25b**: R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$	**25a** 55 **25b** 60
5	**21a/b**	PhSNa, DMF, reflux, 1 h	 **26a**: R^1 = Me, R^2 = Ph **26b**: R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$	**26a** 20 **26b** 31

[a] Isolated yield.



Scheme 5. Reagents, conditions and yields: (i) H_2, 10% Pd/C, MeOH, 2 h, 85%; (ii) H_2, 10% Pd/C, MeOH, 1 h, 95%.

of benzylic hydrogenolysis as well as the utilization of this methodology in the synthesis of DNA minor-groove binding agents bearing additional polar substituents will be reported in due course.

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24. *Data for* **21a**: δ_H (300 MHz, $CDCl_3$) 2.04 (3H, s, $NHCOCH_3$), 2.96 (3H, s, SO_2CH_3), 5.06 (2H, s, $ArCH_2O$), 7.32 (1H, br s, Ar-H), 7.38–7.43 (2H, m, Ar-H), 7.48–7.50 (2H, m, Ar-H), 7.80–7.83 (2H, m, Ar-H), 7.93 (1H, s, Ar-H), 8.27 (1H, s, NH) and 8.59 (1H, s, NH). δ_C (75 MHz, $CDCl_3$) 24.3 (CH_3, $NHCOCH_3$), 38.1 (CH_3, OSO_2CH_3), 71.21 (CH_2, $ArCH_2O$), 112.6 (CH, Ar-C), 115.6 (CH, Ar-C), 115.9 (CH, Ar-C), 127.2 (CH, Ar-C), 128.7 (CH, Ar-C), 132.0 (CH, Ar-C), 134.4 (quat. Ar-C), 134.9 (quat. Ar-C), 139.0 (quat. Ar-C), 139.2 (quat. Ar-C), 166.4 (C=O, NHBz) and 169.3 (C=O, NHAc). Found M^+ 362.09371, $C_{17}H_{18}N_2O_5S$ requires 362.09364.
25. *General procedure for the displacement reaction of benzylic mesylates*: To a solution of mesylate (1 mmol) in dry DMF (2 ml) or dry THF (3 ml) was added the appropriate nucleophile (3 mmol) and the mixture stirred at room temperature until no starting material was visible on the tlc. Ethyl acetate was added (20 ml) and the mixture washed with water (2×20 ml) and brine (20 ml), dried ($NaSO_4$), filtered and the solvent removed in vacuo to afford the crude product, which was purified by flash silica chromatography to afford the desired benzylic amine, ether or sulfide.
26. *Data for* **29**: δ_H (400 MHz, CD_3OD) 2.11 (3H, s, $NHCOCH_3$), 3.74 (2H, s, $ArCH_2NH_2$), 7.32 (1H, br s, Ar-H), 7.36 (1H, br s, Ar-H), 7.46–7.50 (2H, m, Ar-H), 7.54–7.58 (1H, m, Ar-H) and 7.89–7.91 (3H, m, Ar-H). δ_C (100 MHz, CD_3OD) 23.9 (CH_3, $NHCOCH_3$), 46.6 (CH_2, $ArCH_2NH_2$), 112.8 (CH, Ar-C), 116.4 (CH, Ar-C), 116.9 (CH, Ar-C), 128.6 (CH, Ar-C), 129.6 (Ch, Ar-C), 132.9 (CH, Ar-C), 136.2 (quat. Ar-C), 140.3 (quat. Ar-C), 140.4 (quat. Ar-C), 144.7 (quat. Ar-C), 168.8 (C=O, NHBz) and 171.7 (C=O, NHAc). Found MH^+ 284.13958, $C_{16}H_{18}N_3O_2$ requires 284.13990.