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Direct, One-Pot Reductive Alkylation of Anilines with Functionalized Acetals Mediated by Triethylsilane and TFA. Straightforward Route for Unsymmetrically Substituted Ethylenediamine

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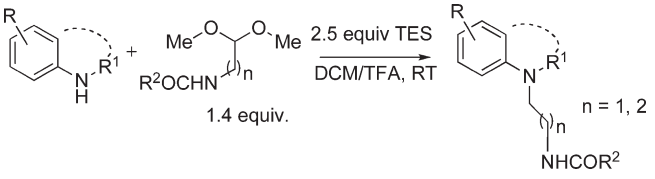

A new, robust, and reliable method has been developed for the selective reductive N-alkylation of primary and secondary aromatic amines with some functionalized acetals using TFA/Et_3SiH as a reagent combination. A variety of unsymmetrically substituted ethylenediamines can be synthesized in a one-pot procedure in excellent yields at room temperature. This new procedure offers significant advantages over previous synthetic approaches, including brevity, mild reaction conditions, excellent yields, and high functional group tolerance.

In support of an ongoing medicinal chemistry research program in the melatonin field[1] aimed at the discovery of new treatments for insomnia, there was a need for developing a safe and scalable synthetic process to supply a number of *N*-diarylaminoalkylamides **1**, a subclass of unsymmetrically substituted ethylenediamines (Figure 1).[2] In particular,

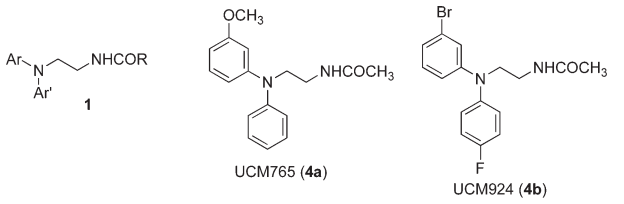

FIGURE 1. General structure of *N*-diarylaminoalkylamides and two representative melatonin ligands.

UCM765 (**4a**) and UCM924 (**4b**) were required in multigram quantities to fulfill preclinical development needs.[3]

Many compounds of pharmaceutical interest have a diarylalkylidendiamine scaffold, so it is of great interest to develop a general, practical, and efficient synthetic procedure to access these substances. It is clear that, wherever possible, it would be desirable to find a step-economical synthesis[4] that does not involve the use of protecting groups[5] and expensive or toxic reagents. Despite the apparent simplicity of the ethylenediamine structure, there are few efficient and selective methods currently available for their preparation. One of the more direct approaches provides for the alkylation of an amine with highly toxic substituted aziridines or their precursors such as *N*,*N*-disubstituted chloroethylamines.[6] On the contrary, 2-oxazolines[7a] and 2-oxazolidinones[7b] can be viewed as less toxic synthetic equivalents of aziridines. Therefore, direct nucleophilic ring-opening at the 5-position of oxazolines with a secondary amine to give β-substituted ethylcarboxamides seemed more attractive. However, in our hands, no more than 34% yield was achieved using different diarylamines and Brönsted acids at 180 °C (Figure 2, approach A).

Alternatively, the desired unsymmetrically substituted ethylendiamines can also be achieved in a multistep sequence. For example, N-acylation with toxic chloroacetylchloride followed by reduction of the amide group, phthalimide alkylation and final deprotection is one strategy. The same product can be obtained in a two-step procedure by N-cyanoalkylation with bromoacetonitrile (in the presence of a strong base) followed by reduction of the nitrile (Figure 2, approach B).[2,8] However, these approaches afforded very low overall yields and were considered not feasible for the preparation of arrays of compounds due to the harsh reducing conditions, security issues, and low functional group tolerance.

(1) For recent examples, see: (a) Mor, M.; Rivara, S.; Pala, D.; Bedini, A.; Spadoni, G.; Tarzia, G. *Expert Opin. Ther. Pat.* **2010**, *8*, 1059–1077. (b) Lucarini, S.; Alessi, M.; Bedini, A.; Giorgini, G.; Piersanti, G.; Spadoni, G. *Chem. Asian J.* **2010**, *3*, 550–554. (c) Spadoni, G.; Bedini, A.; Diamantini, G.; Tarzia, G.; Rivara, S.; Lorenzi, S.; Lodola, A.; Mor, M.; Lucini, V.; Pannacci, M.; Caronno, A.; Fraschini, F. *ChemMedChem* **2007**, *12*, 1741–1749.

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(8) Lucini, V.; Pannacci, M.; Scaglione, F.; Fraschini, F.; Rivara, S.; Mor, M.; Bordi, F.; Plazzi, P. V.; Spadoni, G.; Bedini, A.; Piersanti, G.; Diamantini, G.; Tarzia, G. *J. Med. Chem.* **2004**, *17*, 4202–4212.

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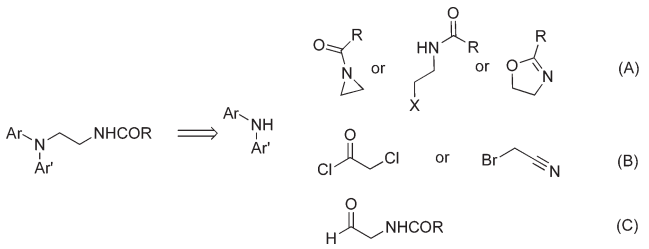

FIGURE 2. Possible approaches to unsymmetrically substituted ethylenediamines.

Direct reductive amination of carbonyl compounds has been widely utilized to prepare amines and offers compelling advantages over other syntheses, including brevity, wide commercial availability of substrates, generally mild reaction conditions, high functional group tolerance, ease of operation, and cost effectiveness. However, reductive amination of poorly reactive, electron-deficient arylamines is known to be difficult. Recent work[9] has shown the synthesis of some ethylendiamines by reductive N-alkylation of suitable primary or secondary N-alkylanilines with commercially available *N*-Boc glycinal, but there are no reports of this protocol using diarylamines as the amine partner (Figure 2, approach C). Indeed, our initial efforts to prepare UCM765 (**4a**) by reacting the diarylamine **2a** with the commercially available *N*-Boc glycinal using $NaBH(OAc)_3$ or $NaCNBH_3$ were thwarted by insufficient imine/iminium concentration and competing direct reduction of the carbonyl group. Even with excess aldehyde, conversion of the amine remained below 10%. The standard literature recommendation for poorly nucleophilic amines is to add acetic acid, along with a concomitant increase in the amounts of carbonyl component and reducing agent.[10] In the present case, poor yields were still obtained with addition of AcOH, although a trend toward increasing yield with increasing quantities of acid was clear. Instead, the same protocol applied to *N*-methylaniline (**2i**) provided the alkylated product in modest yield (ca. 30%).

Decaborane[11a] and a polymethylhydrosiloxane (PMHS)/TFA combination system[11b] have been recently used for the successful one-pot reductive amination of benzaldehyde dimethyl acetal with primary aromatic amines. Therefore, we evaluated the possibility of extending these methodologies to diarylamine **2a** with the functionalized acetal *N*-(2,2-dimethoxyethyl)acetamide (**3a**).

While using decaborane no reaction occurred, using PMHS and TFA in CH_2Cl_2 at room temperature, the desired product was obtained in very poor yields. Despite these disappointing results, we still believed that hydrosilanes in the presence of a strong Brönsted acid such as TFA should be effective for our purposes.[12] Indeed, when triethylsilane (2.5 equiv) was added to a solution containing 3-methoxy-*N*-phenylaniline (**2a**) (1.0 equiv) and *N*-(2,2-dimethoxyethyl)acetamide (**3a**) (1.4 equiv) in CH_2Cl/TFA (2:1), the desired tertiary amine UCM765 (**4a**) was formed smoothly.[13] In 2 h at room temperature, the reaction was complete and the product **4a** was isolated in 93% yield (Table 1, entry 1). The same reaction conditions when applied to 3-bromo-*N*-(4-fluorophenyl)aniline (**2b**) gave the alkylated product UCM924 (**4b**) in excellent yield (Table 1, entry 2). It is also worth noting that debrominated side product was not detected by LC−MS in the crude mixture, demonstrating that these reaction conditions are mild and selective. A number of other diarylamines having therapeutically relevant scaffolds (**2c**−**f**) were tested with this new method (Table 1, entries 3−6). The biological activity manifested by tricyclic, nitrogen containing heterocyclic compounds makes them attractive substrates to test the reaction. Thus, dibenzazepine **2c**, dihydrodibenzazepine **2d**, carbazole **2e**, and phenothiazine **2f** were subjected to the above reductive N-alkylation conditions, and the corresponding N-alkylated products **4c**−**f** were obtained in high yields (85−95%). Notably, **2d** reacted readily and in high yield under these reaction conditions, while no reaction has been reported under standard reductive amination conditions even with aldehydes.[10] In certain instances, the reductively alkylated products could be directly crystallized in high purity following aqueous workup. When the products were oils, chromatography was necessary to obtain analytically pure material. In general, however, the crude products from these reductive alkylations were sufficiently clean that a short filtration was enough to have analytically pure product. We then explored reductive N-alkylation reactions of *N*-(2,2-dimethoxyethyl)-acetamide with different *N*-alkylanilines, as illustrated in Table 1 (entries 7−11), including some partially saturated bicyclic heterocycles such as indoline and tetrahydroquinoline (entries 7 and 8); all reacted smoothly to generate the desired products in good to excellent yields. It is noteworthy to observe that 4-nitro-*N*-methylaniline (**2j**), underwent successful alkylation (95% yield), with no reduction of the nitro group, further highlighting the remarkable chemoselective character of the reducing system (Table 1, entry 10). Unfortunately, no reaction occurred when *N*-isopropylaniline was used (Table 1, entry 11), whereas an acceptable yield was obtained when the carbamate was used as the amine partner (Table 2 entry 7). Having secured access to a range of tertiary amines, attention was focused on the application of the same conditions to primary anilines.

It was found that anilines bearing both electron-withdrawing groups (nitro, ester, or cyano) and/or electron-donating groups were alkylated smoothly in high yields (Table 2) with functional groups such as NO_2, CF_3, CO_2Me,

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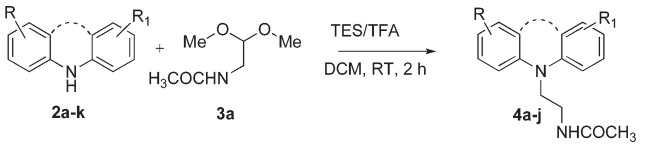
(13) For other use of the triethylsilane in reducing reactions, see: (a) Dubè, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295–2298. (b) Lee, O.-Y.; Law, K.-L.; Ho, C.-Y.; Yang, D. *J. Org. Chem.* **2008**, *73*, 8829–8837. (c) Mizuta, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 2195–2199. (d) Lucarini, S.; Bedini, A.; Spadoni, G.; Piersanti, G. *Org. Biomol. Chem.* **2008**, *6*, 147–150. For an elegant study demonstrating that organosilanes are weaker hydride donors, see: Richter, D.; Mayr, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1958–1961.

TABLE 1. Reductive N-Alkylation of Secondary Anilines with *N*-(2,2-Dimethoxyethyl)acetamide[a]



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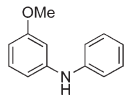
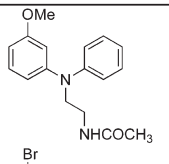
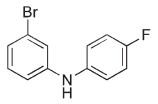
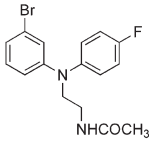
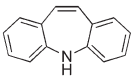
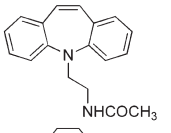
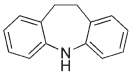
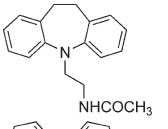
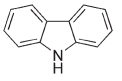
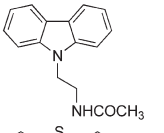
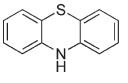
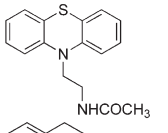
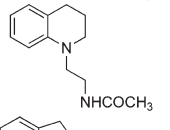
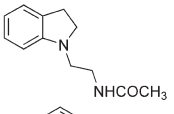
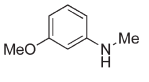
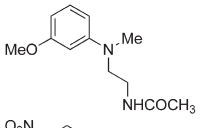
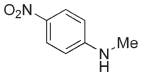
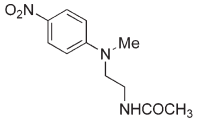
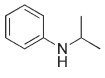
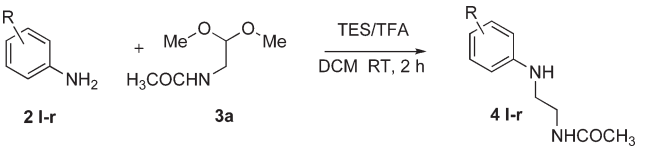
1	a			93
2	b			90
3	c			95
4	d			92
5	e			85
6	f			87
7	g			66
8	h			54
9	i			51[c]
10	j			96
11	k		-	NR[d]

[a]All reactions were performed at room temperature for 2 h with 1.4 equiv of acetal, 1.0 equiv of amine, and 2.5 equiv of Et_3SiH in CH_2Cl_2/TFA 2:1 (0.25 M). [b]Isolated yields. [c]16 h at room temperature. [d]NR: no reaction.

Cl, CN, OCH_3, $HNCOCH_3$, and double bonds remaining unaffected. Furthermore, the results in Table 2 show that this procedure performs well also in cases that caused difficulties for other reductive amination. In particular, substrates with

TABLE 2. Reductive N-Alkylation of Primary Anilines and Benzylcarbamate with *N*-(2,2-Dimethoxyethyl)acetamide[a]



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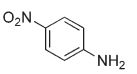
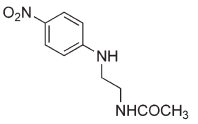
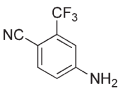
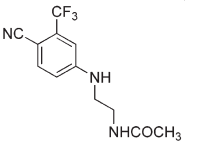
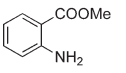
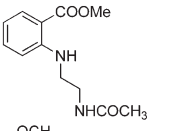
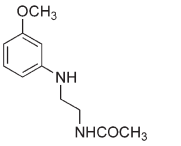
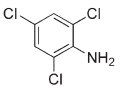
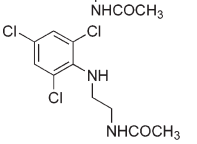
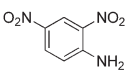
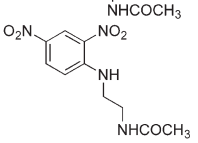
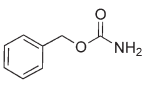
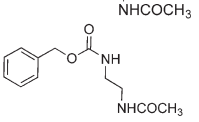
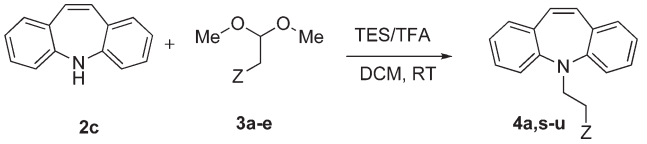
1	l			95
2	m			63
3	n			97
4	o			92
5	p			85
6	q			57[c]
7	r			51

[a]All reactions were performed at room temperature for 2 h with 1.1 equiv of acetal, 1.0 equiv of amine, and 2.5 equiv of Et_3SiH in CH_2Cl_2/TFA 2:1 (0.25 M). [b]Isolated yields. [c]16 h at room temperature.

poor nucleophilicity and/or steric inaccessibility, such as 2,4-dinitro- and 2,4,6-trichloroanilines react either very slowly or show no reaction under the standard reductive amination conditions.[10] On the contrary, these weakly basic anilines when subjected under our conditions provided the desired amides **4q** and **4p** in good yields. The ability to use primary aromatic amines under these acid-promoted conditions is notable since the competitive reactions involving the resulting secondary amines and the starting carbonyl/acetal has been reported to be a significant issue. Having demonstrated that both primary and secondary anilines undergo reductive N-alkylation with acetamidoacetaldehyde dimethyl acetal, we then briefly investigated different functionalized acetals (Table 3). The results for reductive N-alkylation of the pharmaceutically widely used 5*H*-dibenzo[*b*,*f*]azepine scaffold with different functionalized acetals are shown in Table 3. The readily available superior homologue of **3a** and acetal **3c** both reacted very well, even though a longer reaction

TABLE 3. Reductive Amination with Various Acetals of 5*H*-Dibenzo[*b*,*f*]azepine



2c **3a-e** **4a,s-u**

entry	Z	time (h)	product	yield[a] (%)
1	$-NHCOCH_3$ (**3a**)	2	**4a**	95
2	$-CH_2NHCOCH_3$(**3b**)	16	**4s**	71
3	$-CN$ (**3c**)	16	**4t**	60
4	$-NHCOCF_3$ (**3d**)	2	**4u**	85
5	$-NH_2$ (**3e**)	48	**4v**[b]	NR[c]

[a]Isolated yields. [b]Amine **4v** was obtained by hydrolysis of **4u** with potassium carbonate in methanol. [c]NR: no reaction.

time was needed (Table 3, entries 2 and 3) demonstrating that this approach can be easily applied to the synthesis of unsymmetrical propylenediamines. Under these optimized conditions, no alkylation occurred with 2,2-dimethoxyethanamine. However, the reaction was successful when the free amino group was protected with the easily cleavable trifluoroacetyl group (Table 3, entry 4). In addition to the alkylation proceeding almost quantitatively, the removal of the trifluoroacetyl group was extremely simple affording the unsymmetrical ethylenediamine with a free amino group ready for further functionalization, in very high yield (Table 3, entry 5).

In summary, an expedient method for the synthesis of unsymmetrically substituted ethylene and propylendiamine is described. An effective and highly chemoselective procedure was developed for the reductive N-alkylation of primary and secondary aniline substrates with different functionalized acetals normally viewed as poor partners in this process. Under these conditions, there is no requirement for a large excess of either the acetal partner or the reducing agent and the conditions are mild enough to tolerate functionalities such as nitro, cyano, ester, double bonds, and halogens. Taken as a whole, the described chemistry outlines a method by which a range of functionalized diamines cores can be rapidly accessed in high yield starting from inexpensive materials with minimal purification. In addition, it provides a convenient alternative to the reported synthesis of substituted ethylenediamines based on aziridine, phthalimide alkylation, or nitrile reduction. The ubiquity of ethylenediamines in natural products combined with the pharmaceutical relevance of this substructure should render this approach broadly useful.

Experimental Section

General Procedure for the Preparation of Unsymmetrically Substituted Ethylenediamines. To a solution of suitable aniline (1 mmol) and acetal (1.4 mmol) in CH_2Cl_2 (2 mL) under nitrogen were added TFA (1 mL) and triethylsilane (TES, 2.5 mmol), and the resulting mixture was stirred at room temperature. The reaction was cooled at 0 °C, carefully neutralized with a saturated solution of $NaHCO_3$, and diluted with CH_2Cl_2. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate as the eluent.

(*Z*)-*N*-(2-(5*H*-Dibenzo[*b*,*f*]azepin-5-yl)ethyl)acetamide, 4c. The general method using 5*H*-dibenzo[*b*,*f*]azepine (193 mg, 1.0 mmol) gave after chromatographic purification **4c** (264 mg, 0.95 mmol) as a yellowish solid: yield 95%; mp 127−128 °C; MS (ESI) 279.1 [M + 1]; IR (film, cm^{-1}) 3262,1635,1570; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.88 (s, 3H), 3.38 (dd, 2H, J = 5, 5.5 Hz), 3.89 (t, 2H, J = 5.5 Hz), 6.05 (br s, 1H), 6.81 (s, 2H), 6.99−7.33 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0, 149.6, 133.9, 132.0, 129.3, 129.2, 124.0, 120.6, 49.6, 36.5, 23.3. Anal. Calcd for $C_{18}H_{18}N_2O$ (278.14): C, 77.67; H, 6.52; N, 10.06. Found: C, 77.71; H, 6.54; N, 10.09.

Methyl 2-(2-Acetamidoethylamino)benzoate, 4n. The general method using methyl 2-aminobenzoate (151 mg, 129 μL, 1.0 mmol) gave after chromatographic purification **4n** (229 mg, 0.97 mmol) as a white solid: yield 97%; mp 107−108 °C (ether); MS (ESI) 237.1 [M + 1]; IR (film, cm^{-1}) 3251, 1734, 1667; ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H), 3.41−3.52 (m, 4H), 3.86 (s, 3H), 5.90 (brs, 1H), 6.66 (dd, 1H, J = 6, 7 Hz), 6.79 (dd, 1H, J = 6, 7 Hz), 7.33 (dd, 1H, J = 7 Hz), 7.80 (brs, 1H), 7.90 (dd, 1H, J = 6, 7 Hz); ^{13}C NMR (acetone d_6) δ 169.5, 168.5, 151.1, 134.6, 131.4, 114.4, 111.3, 109.9, 50.8, 41.9, 38.4, 22.0; Anal. Calcd for $C_{12}H_{16}N_2O_3$ (236.1): C, 61.00; H, 6.83; N, 11.86. Found: C, 61.06; H, 6.81; N, 11.81.

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Supporting Information Available: Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.