Novel and Highly Regioselective Friedel–Crafts Alkylation of 3,5-Dimethoxyaniline Using an Aldehyde and Triethylsilane as Reducing Agent

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Abstract: A novel and highly regioselective Friedel–Crafts alkylation, producing *p*-alkyl 3,5-dimethoxyanilines by the reaction of aldehydes with 3,5-dimethoxyaniline in the presence of trifluoroacetic acid and triethylsilane as reducing agent is reported. This procedure is lauded by its high regioselectivity, simplicity, and adaptability to aromatic, heteroaromatic, and aliphatic aldehydes. This reaction represents a useful way to prepare a variety of 4-substituted 3,5-dimethoxyanilines of potential pharmacological interest.

Key words: Friedel–Crafts alkylation, regioselective, triethylsilane, activated aniline, nucleophilic

Activated anilines are synthetically versatile substrates in organic chemistry, as they possess multiple nucleophilic sites. 3,5-Dimethoxyaniline is a classical example of activated anilines, where it is proven to be a versatile building block for the construction of molecules that possess antimitotic activity,[1] protein kinase inhibitory activity,[2] and as key intermediate in the synthesis of selective estrogen receptor beta modulators.[3] The reaction of 3,5-dimethoxyaniline and ninhydrin was reported to produce interesting and synthetically useful products.[4] Barbara Roth and coworkers have reported the use of *para*-alkyl 3,5-dimethoxyaniline for the construction of trimethoprim analogues (Figure 1) which are found to possess antimicrobial activity.[5]

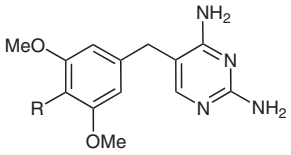


Figure 1 Trimethoprim (R = OMe)

In our recent studies toward the synthesis of trimethoprim analogues, we were interested to prepare various *para*-alkyl 3,5-dimethoxyanilines as building blocks, which could be further utilized for the construction of trimethoprim analogues. During our research, we realized that there are few practical methods to introduce an alkyl-C4 substituent on 3,5-dimethoxyaniline. Although the synthesis of *para*-methyl and *para*-ethyl 3,5-dimethoxyanilines have been reported by Barbara Roth and coworkers via a multistep reaction,[5] the lack of an efficient method to prepare the other alkyl analogues prompted us to develop a practical process for the synthesis of these key intermediates. To our interest, Roth and Kok have claimed that substitution *para* to the amino group occurs in activated anilines.[6] Similarly, Black and co-workers have reported the formation of symmetrical *para*-substituted product in aqueous solvent (Figure 2), while working with 3,5-dimethoxyaniline and ninhydrin.[4]

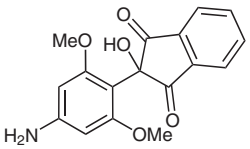
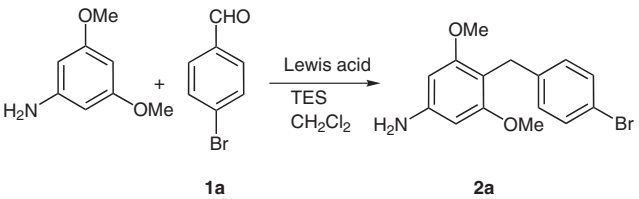


Figure 2

We envisioned that these observations could be exploited to synthesize *para*-alkyl 3,5-dimethoxyanilines by reacting an aldehyde with 3,5-dimethoxyaniline under Friedel–Crafts alkylation conditions. Herein we report on the first high-yielding, highly regioselective, one-pot process for rapid access to *para*-alkyl 3,5-dimethoxyanilines via the sequence of a novel Friedel–Crafts alkylation reaction of an aldehyde with 3,5-dimethoxyaniline induced by TFA and triethylsilane as reducing agent.

Our study began with reacting 3,5-dimethoxyaniline with 4-bromobenzaldehyde (**1a**). When a mixture of 3,5-dimethoxyaniline (1 equiv) and **1a** (1 equiv) in CH_2Cl_2 was treated with one equivalent of $AlCl_3$ and one equivalent of triethylsilane at 25 °C, the aldehyde was consumed in five hours, to afford **2a** in 16% yield in addition to recovered 3,5-dimethoxyaniline (Scheme 1).



1a **2a**

Scheme 1

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Screening a variety of Lewis acids (Table 1, entries 1–7) showed that $InCl_3$, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, $AlMe_3$, $TiCl_4$, and $Mg(ClO_4)_2$ all led to similar yields of **2a**, but interestingly, when TFA (1 equiv) was employed instead of Lewis acids, the aldehyde was consumed in four hours to provide **2a** in 57% isolated yield. Thus it was of interest to gain further insight into the role of the trifluoroacetic acid.

Table 1 Screening of Lewis Acids for the Formation of **2a**

Entry	Lewis acid[a]	Time (h)	Yield of **2a** (%)[b]
1	$AlCl_3$ (1.0)	5	16 (63)
2	$InCl_3$ (1.0)	5	17 (70)
3	$Sc(OTf)_3$ (1.0)	5	9 (82)
4	$BF_3{\cdot}OEt_2$ (1.0)	7	11 (78)
5	$AlMe_3$ (1.0)	4	14 (70)
6	$TiCl_4$ (1.0)	4	16 (66)
7	$Mg(ClO_4)_2$ (1.0)	5	21 (70)
8	TFA (1.0)	4	57 (24)
9	TFA (2.0)	1	93

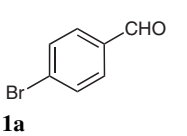
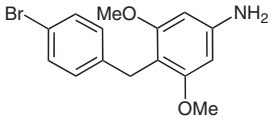
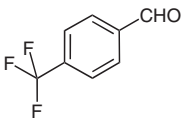
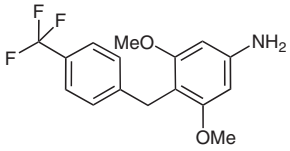
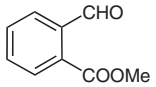
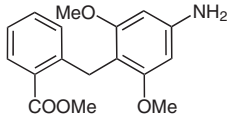
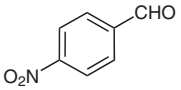
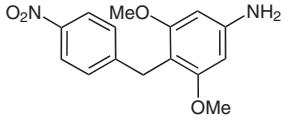
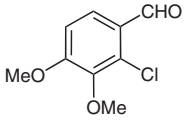
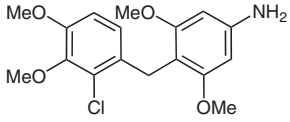
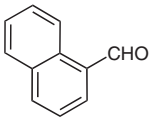
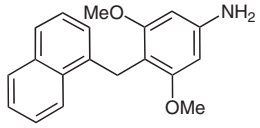
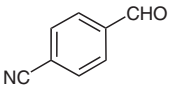
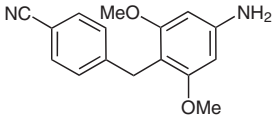
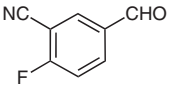
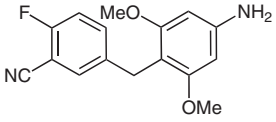
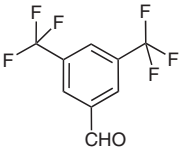
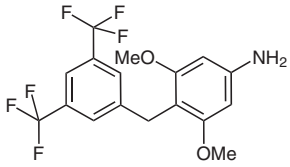
[a] The amount of Lewis acid used is shown in parentheses.
[b] Yield in parentheses is that of recovered 3,5-dimethoxyaniline.

After some reaction optimization such as performing the reaction in a mixture of dichloromethane and TFA (1:1) and use of varying equivalents of TFA and triethylsilane, we were able to conclude that use of TFA (2 equiv) and triethylsilane (2 equiv) in CH_2Cl_2 at room temperature indeed was the ideal method to achieve optimum yield (93%) in shorter duration (Table 2, entry 1).

With the optimal reaction conditions in hand, we proceeded to explore the scope and generality of this reaction. Various easily accessible aromatic aldehydes (**1b–i**) were reacted with 3,5-dimethoxyaniline under the standard conditions to obtain corresponding *para*-alkyl 3,5-dimethoxyanilines in good yields (Table 2). In most cases, the products obtained did not require further purification and were obtained as solids. As depicted in Table 2, aldehydes bearing multiple functional groups did not differ in reactivity and provided the corresponding *para*-substituted 3,5-dimethoxyanilines in excellent yield. In general, all aromatic aldehydes behaved well in the reaction but mixed results were obtained with heteroaromatic aldehydes (Table 3, **1j–p**). While nitrogen heterocycles such as pyridine (Table 3, entries 1–3), quinoline (Table 3, entry 6), imidazole, and thiazole behaved well in the reaction, to our surprise, thiophene (Table 3, entry 7) decomposed completely within minutes of addition of triethylsilane to provide a tarry substance. This could be attributed to the reduction of thiophene system to thiolane under the above reaction conditions.[7]

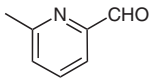
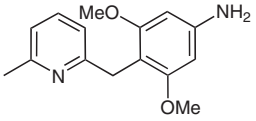
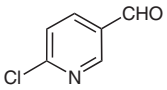
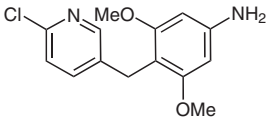
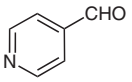
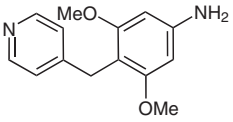
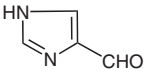
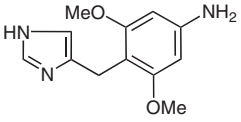
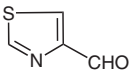
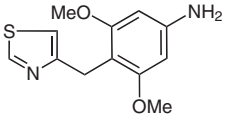
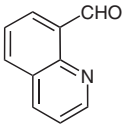
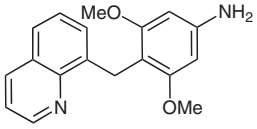
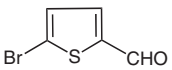
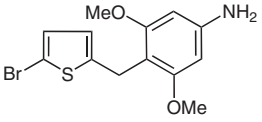
We next examined the application of this protocol to aliphatic aldehydes (Table 4, entries 1–7). The reaction performed very well on all the substrates we tried. While yield of products were excellent with purely aliphatic aldehydes, aliphatic aldehyde with an aromatic tail (Table 4, entry 7) gave only moderate yield.

Table 2 Reaction of Aromatic Aldehydes with 3,5-Dimethoxyaniline

Entry	Substrate	Product	Yield (%)[a]
1	 **1a**	 **2a**	93
2	 **1b**	 **2b**	87
3	 **1c**	 **2c**	85
4	 **1d**	 **2d**	89
5	 **1e**	 **2e**	86
6	 **1f**	 **2f**	91
7	 **1g**	 **2g**	94
8	 **1h**	 **2h**	88
9	 **1i**	 **2i**	90

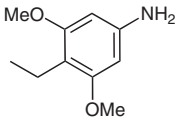
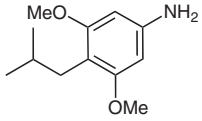
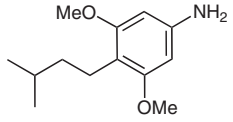
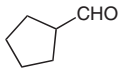
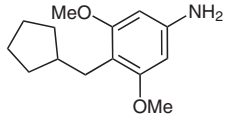
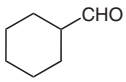
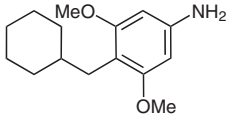
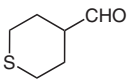
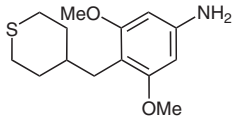
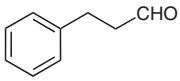
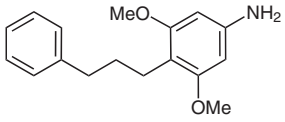
[a] Isolated yields.

Table 3 Reaction of Heteroaromatic Aldehydes with 3,5-Dimethoxyaniline

Entry	Substrate	Product	Yield (%)[a]
1	 **1j**	 **2j**	85
2	 **1k**	 **2k**	86
3	 **1l**	 **2l**	90
4	 **1m**	 **2m**	88
5	 **1n**	 **2n**	87
6	 **1o**	 **2o**	91
7	 **1p**	 **2p**	0[b]

[a] Isolated yields.
[b] No product was isolated. Reaction mass turned into black tar within minutes of addition of triethylsilane.

Table 4 Reactions of Aliphatic Aldehydes with 3,5-Dimethoxyaniline

Entry	Substrate	Product	Yield (%)[a]
1	MeCHO **1q**	 **2q**	89
2	*i*-PrCHO **1r**	 **2r**	89
3	*i*-BuCHO **1s**	 **2s**	88
4	 **1t**	 **2t**	90
5	 **1u**	 **2u**	93
6	 **1v**	 **2v**	94
7	 **1w**	 **2w**	81

[a] Isolated yields.

Further, we examined if we could extend this methodology to other activated anilines. Thus, 3,5-dimethylaniline, 3,5-dichloroaniline, and 3-methoxyaniline were reacted with 4-bromobenzaldehyde under the standard reaction conditions. In all these cases, we found only the N-alkylation product. Similarly, *N*,*N*-dimethyl-(3,5-dimethoxy)aniline did not react with 4-bromobenzaldehyde under the same reaction conditions. We now wish to report that such transformation is general in scope among the reactions we examined for 3,5-dimethoxyaniline, but could be limited to highly electron-rich anilines. In general, the reaction of aromatic or aliphatic aldehydes (1 equiv) and 3,5-dimethoxyaniline (1 equiv) in dichloromethane containing trifluoroacetic acid (2 equiv) and triethylsilane (2 equiv), at room temperature for 1–2 hours, affords *para*-substituted 3,5-dimethoxyanilines in good yields, and the chemistry is highly regioselective. Preferential electrophilic substitution at C4 is probably related to the formation of anilinium salt of the amino group with trifluoroacetic acid, resulting in a steric impediment to attack at C2.

To conclude, we have unveiled a novel and highly regioselective, Friedel–Crafts alkylation of 3,5-dimethoxyaniline, using an aldehyde and triethylsilane as reducing agent.[8] The method is convergent and avoids the synthesis of complicated precursors giving a high level of complexity in single step. This novel finding provides an interesting insight into chemistry of electron-rich anilines and represents a very useful way to prepare *para*-alkyl 3,5-dimethoxyanilines of potential pharmacological interest.

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(8) **Representative Procedure for the Synthesis of 2a**
To a mixture of 4-bromobenzaldehyde (10 g, 0.054 mol) and 3,5-dimethoxyaniline (8.26 g, 0.054 mol) in CH_2Cl_2 (60 mL) was added TFA (12.30 g, 0.108 mol), and the mixture was stirred at r.t. for 10 min. To this was added TES (12.5 g, 0.108 mol) in drops over a period of 10 min, and the reaction was stirred at r.t. for additional 2 h. The completion of reaction was confirmed by TLC (2% MeOH in CH_2Cl_2). The solvent was removed under vacuum and the residue was diluted with H_2O (50 mL) and washed with hexane (2 × 50 mL). The aqueous phase was basified with sat. aq solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phase was washed with H_2O (1 × 100 mL), brine (1 × 50 mL), and dried over Na_2SO_4. The solvent was removed under vacuum to afford 16 g (93%) of 4-(4-bromobenzyl)-3,5-dimethoxyaniline(**2a**) as an off-white solid; mp 167.9–169.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36–7.34 (d, 2 H, *J* = 8 Hz), 7.04–7.02 (d, 2 H, *J* = 8 Hz), 5.89 (s, 2 H), 5.24 (br s, 2 H), 3.65 (s, 2 H), 3.63 (s, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.6, 148.8, 142.3, 131.1, 130.7, 118.4, 104.0, 91.0, 55.6, 27.6. MS (ESI-APCI): *m/z* found for $C_{15}H_{16}BrNO_2$: 324 $[M + 2]^+$. Anal. Calcd (%) for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01, N, 4.35. Found: C, 55.99; H, 5.05, N, 4.28.