ORGANIC LETTERS

2010
Vol. 12, No. 7
1492−1495

Rearrangement Strategy for the Synthesis of 2-Aminoanilines

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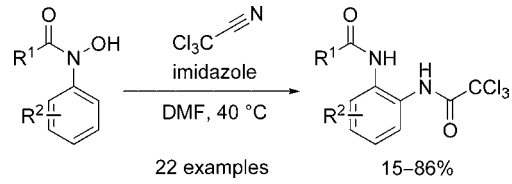
Received January 26, 2010

ABSTRACT



Treatment of *N*-aryl hydroxylamines with trichloroacetonitrile in the presence of imidazole provides a simple and effective method for the preparation of synthetically versatile 2-aminoanilines. Reactions proceed in DMF at 40 °C, providing the products in up to 86% isolated yield.

The 2-aminoaniline scaffold has exceptional industrial significance and is embedded in the structure of a number of important pharmaceuticals. For example, Nexium, Zyprexa, and Alphagan P (Figure 1), which contain this group, had combined worldwide sales in excess of $6.5 billion in 2008.[1] Due to the fact that the structure serves as a precursor to a number of pharmacophores including benzimidazoles,[2] 1,5-benzodiazepines,[3] quinoxalines,[4] benzotriazoles,[5] and benzimidazolones,[6] among others, simple methods for the selective introduction of this group have great synthetic potential.

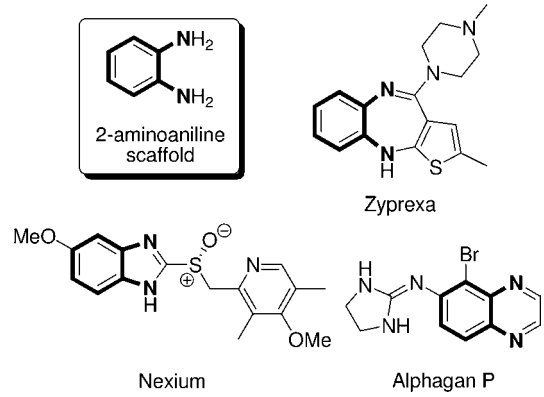


Figure 1. The 2-aminoaniline scaffold in important pharmaceuticals.

Methods for the selective amination of monosubstituted aromatics are scarce, which severely restricts the potential of the 2-aminoaniline core in drug discovery programs with

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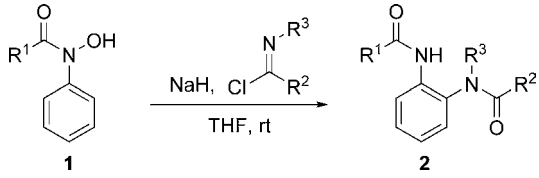
10.1021/ol100196a
Published on Web 03/03/2010

respect to novelty and diversity. An isolated report by Blechert showed that *N*-aryl hydroxylamines (e.g., **1**) can be converted to the *ortho*-functionalized derivative **2** by deprotonation with sodium hydride followed by treatment with imidoyl chlorides (Scheme 1).[7] Although the examples in this report were limited, it is surprising this potentially useful rearrangement has not been exploited.[8] Reasoning the synthetic applicability of this approach could be significantly enhanced by removing the air-sensitive nature of both reactant and reagent we set out to develop this rearrangement further. Within this paper we describe a simple and effective method for the conversion of *N*-aryl hydroxylamines to differentially protected 1,2-diaminobenzenes in a controlled and efficient manner.

Scheme 1. Blechert Synthesis of 2-Aminoanilines

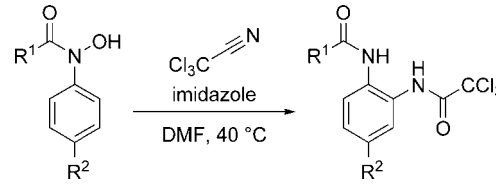


The *N*-aryl hydroxylamines used within this study were prepared from either nitroarenes[9] or aryl halides[10] by known methods, were amenable to scale-up, and had good functional group tolerance. The considerable number of commercially available nitroarenes and aryl halides suggest the technology described will allow for the synthesis of a wide variety of 2-aminoanilines.

As a starting point we examined the reaction of hydroxylamine **3** (R^1 = OMe; R^2 = H) with trichloroacetonitrile varying base, solvent, and temperature. Optimized conditions involved reaction of hydroxylamine **3** with trichloroacetonitrile (4 equiv) in the presence of imidazole (1.05 equiv) in DMF at 40 °C for 6 h, which gave 2-aminoaniline **9** in a pleasing 70% isolated yield (Table 1, entry 1). This represents an operationally simple method for the preparation of differentially protected 2-aminoanilines that proceeds under mild reaction conditions without the need for rigorous exclusion of moisture and air.

In order to determine some of the scope of this transformation, we investigated the effect of changing the nitrogen protecting group on the substrate (Table 1). Three common carbamate protecting groups were examined (Boc, Cbz, and methoxycarbonyl) due to their widespread use in synthesis.

Table 1. Variation of N-Protecting Group[a]



entry	substrate	R^1	R^2	product	% yield[b]
1	**3**	OMe	H	**9**	70
2	**4**	OMe	Me	**10**	80
3	**5**	OBn	H	**11**	62
4	**6**	OBn	Me	**12**	76
5	**7**	O^{t}Bu	H	**13**	73
6	**8**	O^{t}Bu	Me	**14**	83

[a] All reactions performed in duplicate at 0.5 M concentration of hydroxylamine, tichloroacetonitrile (4 equiv), imidazole (1.05 equiv), DMF; 40 °C, 6 h. [b] Isolated yield.

Each of these groups worked with equal efficiency (62−83%) with the *N*-aryl hydroxylamines examined.

Assessment of functional group tolerance and regiochemical course of the rearrangement is outlined in Table 2. In the development of this chemistry, we were concerned with incorporation of useful synthetic handles within the substrates. Chlorides (entry 1; 59%), bromides (entry 2; 45%), and protected phenols (entries 3 and 4; 82% and 79%,

Scheme 2. Transformations of Products

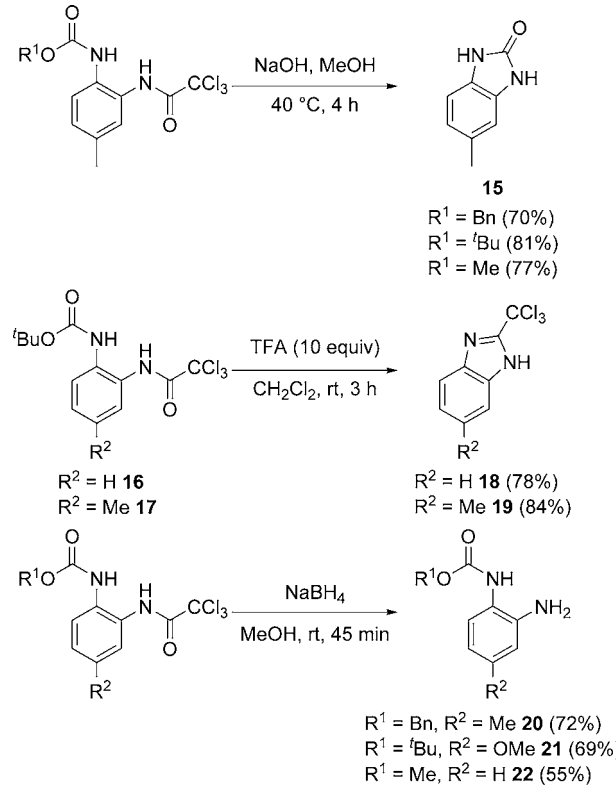


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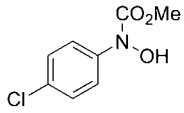
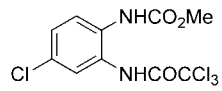
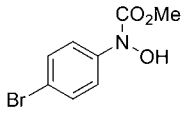
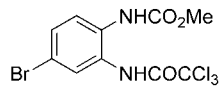
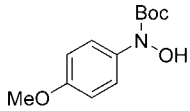
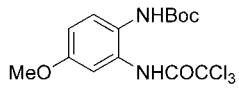
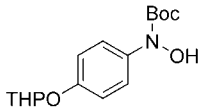
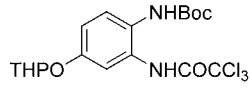
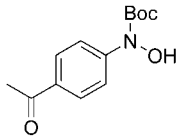
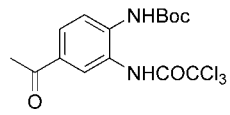
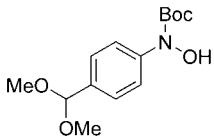
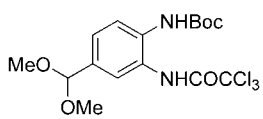
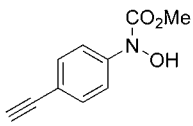
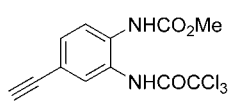
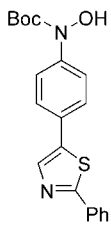
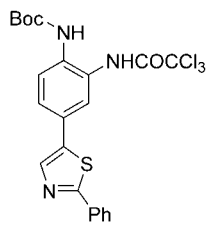
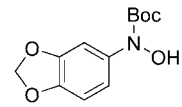
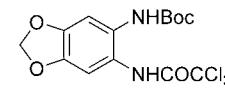
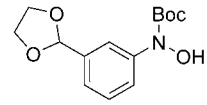
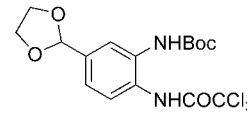
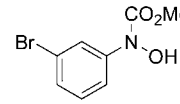
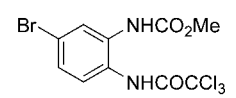
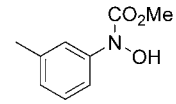
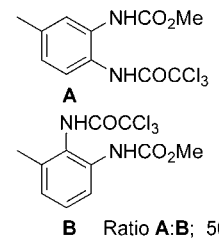
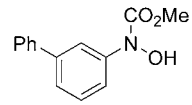
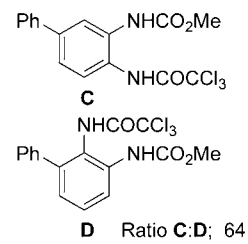
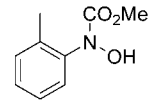
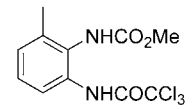
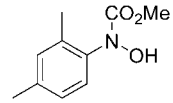
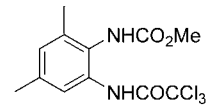
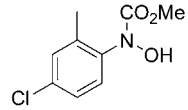
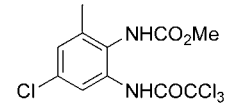
Table 2. Scope of Rearrangement[a]

entry	*N*-aryl hydroxylamine	product	% yield[b]
1			59
2			45
3			82 (79)[c]
4			79
5			15[d]
6			68
7			66
8			67
9			65
10			66
11			49
12		 **A** **B** Ratio **A**:**B**; 56:44	75
13		 **C** **D** Ratio **C**:**D**; 64:36	62
14			62
15			86
16			83

[a] All reactions performed in duplicate at 0.5 M concentration of hydroxylamine, tichloroacetonitrile (4 equiv), imidazole (1.05 equiv), DMF, 40 °C, 6 h. [b] Isolated yield. [c] Reaction performed at room temperature. [d] Conversion based on ^{1}H NMR spectroscopy of crude reaction mixture in $CDCl_3$.

respectively) were tolerated on the aromatic ring. Unprotected carbonyl groups were not effective substrates under the optimized conditions (entry 5; ~15%); however, this could be circumvented by protection as the acetal (entry 6; 68%; entry 10; 66%). Introduction of the versatile alkyne functionality was possible (entry 7; 66%), and common heterocycles such as thiazole were also tolerated (entry 8; 67%). We also examined regiochemical aspects of the rearrangement process (entries 9−14). With larger substituents in the 3-position of the aromatic ring the rearrangement proceeded regioselectively (entries 9−11). Introduction of smaller groups reduced this selectivity such that with a 3-methyl-substituted *N*-aryl hydroxylamine the ratio of products fell to around 1:1 (entry 12). 2-Substitution of the substrates was also well tolerated, providing the expected products in good yield (entries 14−16; 62−86%).

The results presented are consistent with the reaction proceeding via addition of the hydroxylamine oxygen to trichloroacetonitrile followed by [3,3] sigmatropic rearrangement. We have no direct evidence to support this proposal, and further investigation would be necessary in order to determine the precise mechanistic course of the transformation.

Finally, some of the potential products from this transformation are outlined in Scheme 2. Direct access to the benzimidazolidinone pharmacophore (e.g., **15**) is easily achieved by prolonged solvolysis (NaOH, MeOH, 40 °C, 4 h) with Boc, Cbz, and methoxy carbamate protecting groups (70−81%). The benzimidazoles **18** (78%) and **19** (84%) can be prepared directly from the rearranged products **16** and **17** under acidic reaction conditions. The trichloromethyl benzimidazole scaffold resulting from this reaction has been used extensively as a versatile synthetic intermediate.[11] Additionally, the less common trichloroacetyl protecting group can be selectively removed in the presence of Cbz (**20**; 72%), Boc (**21**; 69%), and methoxy (**22**; 55%) carbamates by treatment with an excess of sodium borohydride at room temperature.[12]

In summary, we have developed an effective method for preparation of the 2-aminoaniline scaffold, a privileged pharmacophore. Substrates for these transformations are easily accessed from aryl halides or nitroarenes, and functional group tolerance on both the nitrogen and aromatic substituents suggests the methodology will provide a robust and practical method with which to address this important chemical challenge. The methodology has distinct advantages over literature precedent due to operational simplicity; the reaction proceeds without purification of solvent or reagents and does not require the rigorous exclusion of either moisture or air.

Acknowledgment. The authors thank the EPSRC and GlaxoSmithKline for financial support and the Mass Spectrometry Service, Swansea, for high-resolution spectra.

Supporting Information Available: Analytical data, experimental procedures, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100196A

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