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A New Practical One-Pot Conversion of Phenols to Anilines

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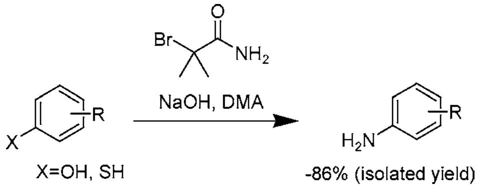
ABSTRACT



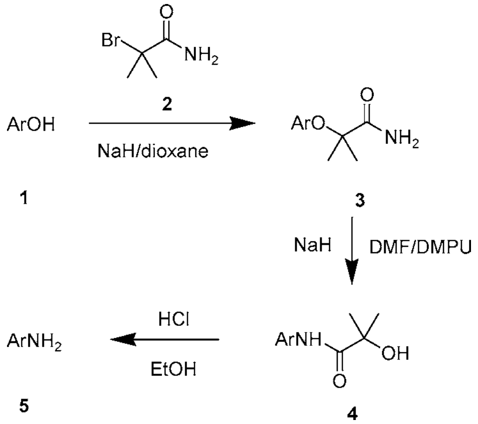
A novel one-pot synthesis of anilines from phenols was developed. Using this methodology, anilines are produced in good yield (86%) by a reaction of phenols with 2-bromo-2-methylpropionamide and NaOH in DMA via Smiles rearrangement. Phenols, which are substituted electron-withdrawing groups, are more reactive for Smiles rearrangement. Thiophenols are also converted to anilines. The process is a convenient, safe, and inexpensive method for large-scale preparation of anilines.

Several methods have been developed for the direct conversion of phenols to anilines, because phenols are generally more available than the corresponding anilines.

These methods include the well-known Bucherer reaction,[1] and activation of phenols with 4-chloro-2-phenylquinazoline[2] or diethyl chlorophosphate.[3] However, all of them suffer from particular drawbacks. The Bucherer reaction is restricted to naphthalenes and related heterocycles, whereas benzene derivatives are much less reactive. Rearrangement of aryloxyquinazoline, prepared from 4-chloro-2-phenylquinazoline, requires extremely high temperatures (ca. 300 °C) and strong basic conditions. Preparation of aryl diethyl phosphate esters requires toxic diethyl chlorophosphate and potassium metal in liquid ammonia.

Another method, which has been used for the conversion of phenols to anilines, is an alkylation−Smiles rearrangement[4]−hydrolysis sequence. (Scheme 1) The phenol **1** was etherified to 2-aryloxy-2-methylpropionamide **3** with 2-bromo-

Scheme 1. Alkylation−Smiles Rearrangement−Hydrolysis Sequence



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(1) (a) Bucherer, H. T. *J. Prakt. Chem.* **1904**, *69*, 49. (b) Wagner, R. B.; Zook, H. D. *Synthetic Organic Chemistry*; John Wiley and Sons: New York, 1953; p 670. (c) Schroter, R. *Houben-Weyl-Muller* **1957**, *11*, 143. (d) Rieche, A.; Seeboth, H. *Ann.* **1960**, *638*, 66.

(2) (a) Morrow, D. F.; Hofer, R. M. *J. Med. Chem.* **1966**, *9*, 249. (b) Conrow, R. B.; Bernstein, S. *Steroids* **1968**, *11*, 151. (c) Scherrer, R. A.; Beatty, H. R. *J. Org. Chem.* **1972**, *37*, 1681. (d) Matsumoto, K.; Stark, P.; Meister, R. G. *J. Med. Chem.* **1977**, *20*, 17. (e) Sadek, S. A.; Shaw, S. M.; Kessler, W. V.; Wolf, G. C. *J. Org. Chem.* **1981**, *46*, 3259.

(3) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1972**, *37*, 3570.

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2-methylpropionamide **2** in dioxane. This underwent Smiles rearrangement to give the *N*-aryl-2-hydroxypropionamide **4**. Then, hydrolysis of **4** gave the aniline **5**.

However, this method also has some difficulties. This sequence consists of a three-step, three-pot process[4e] or a three-step, two-pot process[4f] and requires sodium hydride and *N*,*N*-dimethylformamide, which has a threat of uncontrollable exothermic reaction.[5]

Recently, palladium-catalyzed amination of aryl sulfonates, e.g., aryl triflates and aryl nonaflates, has been investigated.[6] However, this method needs to derive aryl sulfonates from phenols and has serious problems with respect to cost and remaining of palladium.

We report herein the development of a novel three-step, one-pot Smiles rearrangement process to prepare anilines from phenols, which have electron-withdrawing groups.

We selected 6-amino-1-tetralone **9** as a target aniline, which is an important intermediate for medicines and chemicals. Until now, aniline **9** has been synthesized by two general synthetic methods.[7,8]

The first of these involves a Friedel−Crafts ring-closure step near the end of the synthesis. β-Benzoylpropionic acid as a starting material is nitrated to give the *meta*-nitro compound and is then reduced to the amine. Acetylation of the amino group and hydrogenolysis of the ketonic oxygen gives the acetamido acid. Friedel−Crafts cyclization gives 6-acetamido-1-tetralone, which is hydrolyzed to aniline **9**.[7]

The alternative synthetic method involves the introduction of ketonic oxygen into the saturated side chain as a key step. Tetralin as a starting material is acetylated to give 6-acetyltetralin and then provides the oxime. Beckmann rearrangement of the oxime gives 6-acetamidetetralin. Selective oxidation gives 6-acetamido-1-tetralone, which is hydrolyzed to aniline **9**.[8]

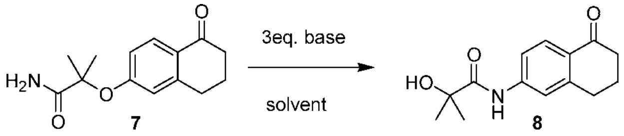
These two general methods require many steps to produce aniline **9**. Our novel three-step, one-pot Smiles rearrangement process should be a very useful method.

The starting compound, 6-hydroxy-1-tetralone **6**, was prepared from commercially available 6-methoxy-1-tetralone quantitatively by acid hydrolysis.

First, we tried the Weidner method,[4f] which is a three-step, two-pot process; then, we confirmed that the alkylation and Smiles rearrangement proceeded successfully. However, the above-mentioned combination of sodium hydride and *N*,*N*-dimethylformamide used in this method could be dangerous.

We have studied the modification of bases and solvents (Table 1) and discovered that an alkali metal hydroxide in a dipolar aprotic solvent, for example, sodium hydroxide in *N*,*N*-dimethylacetamide (DMA), is a mild and safe combination for the Smiles rearrangement. Furthermore, we found that the combination of an alkali metal hydroxide in a dipolar aprotic solvent is successful not only in the Smiles rearrangement but also in the O-alkylation and the hydrolysis reaction. As a result, it is possible to make a three-step process in one-pot.

Table 1. Reaction Conditions of Smiles Rearrangement



entry	base	solvent	temp./time	yield (%)[a] 7	yield (%)[a] 8
1	NaH	DMA	rt/0.5 h	nd[b]	89
2	NaOH	DMA	rt/0.5 h	22	73
3	NaOH	DMA	rt/2 h	nd	94
4	NaOH	MeOH	rt/2 h	96	0.3
5	NaOH	MeOH	reflux/2 h	75	13
6	NaOMe	MeOH	rt/2 h	98	0.1
7	NaOMe	MeOH	reflux/1 h	56	26
8	Na_2CO_3	DMA	rt/2 h	99	nd
9	Na_2CO_3	DMA	140 °C/1 h	27	72

[a] Yield based on quantitative HPLC analysis. [b] nd = not detected.

The phenol **6**, 3 equiv of 2-bromo-2-methylpropionamide **2**, and 3 equiv of sodium hydroxide in DMA were stirred at room temperature to produce 2-aryloxy-2-methylpropionamide **7**. Sodium hydroxide (9 equiv) was added to this solution, and then the mixture was stirred at 50 °C to produce *N*-aryl-2-hydroxypropionamide **8**. Water was added to this solution, and then the mixture was refluxed to produce the aniline **9**. At the end of the reaction, addition of water gave a 59% yield of **9**, which crystallized directly from the reaction solution. (Scheme 2)

We isolated **7** and **8**, which are novel intermediates, by addition of water in each step of the reaction mixture. We obtained a 47% yield of **7** and a 76% yield of **8**, which crystallized directly from the reaction solution mixture.

N-Aryl-2-hydroxypropionamide **8** is an amino-protected compound of aniline **9**, which allows us to modify and later hydrolyze **8**.

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(5) (a) Buckley, J.; Webb, R. L.; Laird, T.; Ward, R. J. *Chem. Eng. News* **1982**, *60* (28), 5. (b) De Wall, G. *Chem. Eng. News* **1982**, *60* (37), 5, 43.

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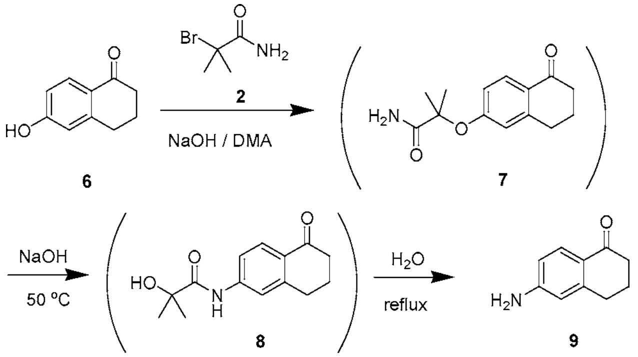
(8) (a) Newman, M. S.; Zahm, H. V. *J. Am. Chem. Soc.* **1943**, *65*, 1097. (b) Schofield, K.; Swain, T.; Theobald, R. S. *J. Chem. Soc.* **1949**, 2399. (c) Allinger, N. L.; Jones, E. S. *J. Org. Chem.* **1962**, *27*, 70. (d) Biggs, D. F.; Casy, A. F.; Chu, Ih; Coutts, R. T. *J. Med. Chem.* **1976**, *19*, 472.

Scheme 2. Novel Synthesis of 6-Amino-1-tetralone[a]



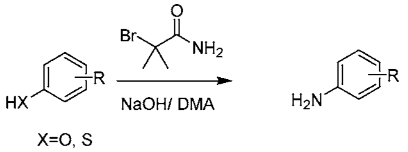
[a] Isolated yield = 59% (three-step, one-pot, only filtration).

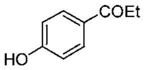
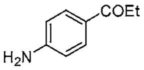
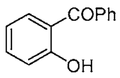
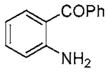
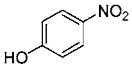
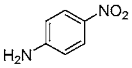
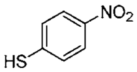
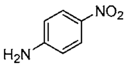
Using our protocol, we were able to produce a variety of phenols or thiophenols. (Table 2) Phenols or thiophenols, which have electron-withdrawing groups, converted to anilines particularly smoothly, and the anilines were isolated in good yield by filtration.

This three-step, one-pot method for the conversion of phenols to anilines is the most convenient, safe, and inexpensive compared to other methods.

In summary, we have described a three-step, one-pot alkylation−rearrangement−hydrolysis procedure for the conversion of 6-hydroxy-1-tetralone **6** to 6-amino-1-tetralone **9**. This is the simplest method to prepare **9**. We then extended this method to the conversion of phenols or thiophenols to anilines, which have electron-withdrawing groups. This method produces a convenient, inexpensive, and scalable method of preparation of anilines. Additional examples of this three-step, one-pot alkylation−rearrangement−hydrolysis procedure will be the subject of a subsequent report.

Table 2. One-Pot Syntheses of Anilines from Phenols (Thiophenols)



entry	substrate	product	conv.[a]	yield[b]
1	 **10**	 **11**	92%	86%
2	 **12**	 **13**	72%	77%
3	 **14**	 **15**	83%	38%
4	 **16**	 **15**	99%	49%

[a] Conversion based on quantitative HPLC analysis (not optimized). [b] Isolated yield (products separated as crystals from reaction mixture by filtration).

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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