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One-pot Conversion of Phenols to Anilines *via* Smiles Rearrangement

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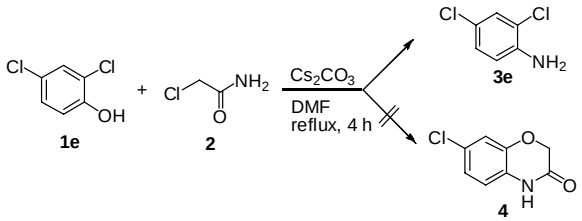
ABSTRACT

A convenient one-pot synthesis of phenols to anilines using 2-chloroacetamide/K_2CO_3/DMF system catalyzed by KI *via* Smiles rearrangement has been described. The synthesis of extensive amino aromatic products from phenols containing electron withdrawing group, has been performed in moderate to excellent yields to demonstrate the potentiality of this method in bio-medicinal and pharmaceutical applications.

Anilines are powerful tools in constructing various heterocyclic systems useful for pharmaceutical and bio-medicinal applications.[1] Several methods have been developed for the direct conversion of phenols to anilines, because phenols are diverse and commercially available starting materials used in industries. These methods include Bucherer reaction,[2] activation of phenols with 4-chloro-2-phenylquinazoline[3] or diethyl chlorophosphate,[4] palladium-catalyzed amination[5] etc. However, all of them have some practical difficulties. The well-known Bucherer reaction is a simple and efficient method to prepare aromatic amines from phenols, but the transformation is generally restricted to the naphthalene system and related heterocycles. Activation of phenols with 4-chloro-2-phenylquinazoline which is an etherification/ rearrangement/ hydrolysis procedure requires extremely high temperature (275-325 ^{o}C) for rearrangement and strong base conditions. Amination of aryl diethyl phosphate esters, prepared from toxic diethyl chlorophosphate, requires potassium metal in liquid ammonia. The palladium-catalyzed amination is an enduring ligand and palladium method and needs to drive aryl sulfonates from phenols that has serious problems with respect to cost, and can't be applied to the halogenoaryl sulfonate because of the competition of cross-coupling between aryl halide and amine.

A method for the direct conversion of phenols to anilines by alkylation/Smiles rearrangement/hydrolysis sequence has already been reported.[6] This method has been exploited to synthesize a series of important amino aromatic compounds, such as 4-amino-benzo[b]thiophen,[6a,6e] *N*-aryl-2-hdroxypropionamides,[6c] 2-bromo-l-naphthylamine,[6d] 6-amino-1-tetralone,[6f] 4-amino-benzofuran,[6g] and 2,3-dihaloanilines.[6h,6i] However, most of these methods often require NaH/dimethylformamide (DMF) system, which has a peril of uncontrollable exothermic reaction conditions.[7] Even though, alternative approaches with NaOH/DMF or NaOH/DMA gave encouraging results to replace hazardous NaH/DMF system, it needs harmless treatment of liquid waste which in turn increases the cost and thus a limitation for large-scale preparation.[6f] So, there is always been a demand for apt method to establish practical synthesis of aryl amines.



Scheme 1. Unexpected conversion of phenols to anilines under Smiles rearrangement conditions

The syntheses of heterocyclic compounds based on Smiles rearrangement including *N*-alkyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives from 2-chlorophenols and *N*-alkyl-2-chloroacetamides have been reported by our group.[8] In continuation of our efforts in the development of simple, eco-friendly and cost-effective methodologies, we herein wish to report a one-pot tandem synthesis of anilines from phenols using 2-chloroacetamide and K_2CO_3 in DMF catalyzed by KI.

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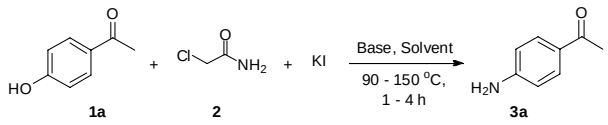
Our initial attempts to extend the research towards design and synthesis of 7-chloro-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**4**) starting from 2,4-dichlorophenol (**1e**) and 2-chloroacetamide (**2**) were failed, instead 2,4-dichloroaniline (**3e)** was isolated exclusively under Cs_2CO_3/DMF reaction conditions as shown in Scheme 1. This conversion can be explained by de-acylation of acylamide, which was formed after *O*-alkylation/Smiles rearrangement sequence. This result encouraged us to explore direct conversion of phenols to anilines as a convenient alternative to the previous methodologies. In addition, DMF can be easily recovered by distillation under reduced pressure and then the residue can be directly purified using silica gel column chromatography, thus avoiding a formal aqueous workup. Various phenols were examined to achieve the corresponding anilines.



Scheme 2. The three-step one-pot synthesis of anilines from phenols

Table 1. Optimization of the conversion of **1a** to **3a**

Entry	Base	Solvent	Conditions	Yield[a] (%)
1	Na_2CO_3	DMF	150 °C, 4 h	0 [b]
2	K_2CO_3	CH_3CN	reflux, 4 h	0[b]
3	Cs_2CO_3	DMF	90 °C, 1 h then 150 °C, 4 h	54
4	K_2CO_3	DMF	90 °C, 2 h then 150 °C, 4 h	63
5	K_2CO_3/KI [c]	DMF	90 °C, 1 h then 150 °C, 4 h	75

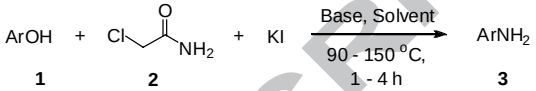
[a]Yields of isolated products
[b]Only 2-(4-acetylphenoxy)acetamide formation was observed
[c]20 mol% of KI to **1a**.

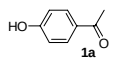
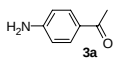
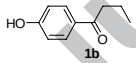
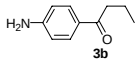
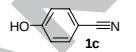
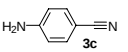
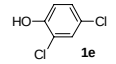
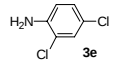
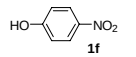
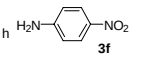
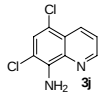
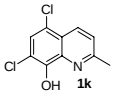
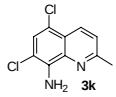
To establish the appropriate reaction conditions, we have chose 1-(4-hydroxyphenyl)ethanone (**1a**) as a phenol substrate and examined the effects of formal bases and solvents (Scheme 2). At first, we examined the reaction of **1a** (1 equiv) with 2-chloroacetamide (1.2 equiv) in DMF in the presence of different bases (2.5 equiv) and the results are summarized in Table 1. Among the three bases we found that K_2CO_3 is the better one when compared with both Cs_2CO_3 and Na_2CO_3. We have also tried the reaction in acetonitrile and were able to isolate only 2-(4-acetylphenoxy)acetamide (in 91% yield) an *O*-alkylated product, may be due to lower boiling point which is not sufficient to induce Smiles rearrangement. Optimal conditions for the preparation of **3a** in 75% yield were identified (Table 1, Entry 5), using the catalyst KI which effectively accelerated the *O*-alkylation process.

The typical experimental procedure involves heating a mixture of phenol (**1**)/$ClCH_2CONH_2$/K_2CO_3/KI in the mole ratio of 1/1.2/2.5/0.2 for 1 h at 90 °C in DMF and then 4 h at 150 °C. Then, the solvent was directly removed under reduced pressure and residue was purified by flash column chromatography to give the corresponding aniline (**3**). The one-pot syntheses of anilines **3a**-**3k** have been performed and the yields of products have been presented in Table 2.

This method describes a facile conversion of simple phenols (Table 2, Entry 1, 2, 3, 6 and 7), chlorophenols (Table 2, Entry 4, 5, 9, 10 and 11, which even include heterocyclic phenols) to their corresponding anilines. It can be seen from the results described in the table 2 (Entry 10 & 11) that the heterocyclic phenols did not avail anilines and not even phenolic *O*-alkylation with K_2CO_3 alone. This describes the importance of catalyst KI in the activation of *O*-alkylation when K_2CO_3 used as a base with all kinds of phenols. It was also observed that phenols having electron-withdrawing substituent on the aromatic ring only accelerated Smiles rearrangement reaction. The phenols that are attached to a heterocyclic ring gave low yields when compared to others. Even though, this method provides the scope to extend the research in the synthesis of substituted amino pyridines (Table 2, Entry 8), which have both chemical and biological significance[9] (neurological diseases, K^+ channel blockers, apoptosis, carcinogenic activity and chronic toxicity etc.) and are starting materials in the production of various drugs.

Table 2. Conversion of various phenols to anilines



Entry	ArOH	Base(s)	Temperature Conditions	Product[a]	Yield (%)[b]
1	 1a	2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 2 h then 150 °C, 4 h	 3a	75
2	 1b	2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 2 h then 150 °C, 4 h	 3b	70
3	 1c	2.5 eq. $CsCO_3$ or 2.5 eq. K_2CO_3 or 2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 2 h then 150 °C, 4 h	 3c	60[c] 69[d] 84
4	 1d	2.5 eq. $CsCO_3$ or 2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 1-2 h then 150 °C, 4 h	 3d	38[c] 65
5	 1e	2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 2 h then 150 °C, 4 h	 3e	62
6	 1f	2.5 eq. $CsCO_3$ or 2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 1-2 h then 150 °C, 4 h	 3f	44[c] 78
7	 1g	2.5 eq. $CsCO_3$ or 2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 1-2 h then 150 °C, 4 h	 3g	50[c] 92
8	 1h	2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 2 h then 150 °C, 4 h	 3h	42
9	 1i	2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 2 h then 150 °C, 4 h	 3i	54
10	 1j	2.5 eq. K_2CO_3 or 2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 2 h then 150 °C, 4 h	 3j	0[d] 56
11	 1k	2.5 eq. K_2CO_3 or 2.5 eq. K_2CO_3/ 0.2 eq. KI	90 °C, 2 h then 150 °C, 4 h	 3k	0[d] 63

[a]Confirmed by ^{1}H NMR and mass spectrometry
[b]Yields of isolated products with K_2CO_3/cat. KI unless mentioned
[c]Yield of product when Cs_2CO_3 used as a base
[d]Yield product when K_2CO_3 used as a base

We further like to emphasize the applicability of our method in improving the reaction yields. For example, the synthesis of 5,7-dichloro-2-methylquinolin-8-amine[10] (**3k**) (Table 2, Entry 11) which is an important key intermediate in the preparation of a series of antiamyloidogeneic agents. Moreover, our one-pot tandem *O*-alkylation/Smiles rearrangement/hydrolysis approach

is more convenient, safe, eco-friendly and cost-effective. All the compounds were confirmed by ^{1}H, ^{13}C NMR and Mass spectroscopic analysis.[11,12] The analytical data of known products 1-(4-aminophenyl)ethanone (**3a**)[11d,f], 1-(4-aminophenyl)butan-1-one (**3b**)[11d], 4-aminobenzonitrile (**3c**)[11c], 2,6-dichloroaniline (**3d**)[11b], 2,4-dichloroaniline (**3e**)[11e], 4-nitroaniline (**3f**)[11c,d], 2-nitroaniline (3g)[11b,c,d] and 2-chloropyridin-3-amine (**3h**)[11a] are identical with the literature.[11] We are presently engaged with the biological evaluation of various aniline derivatives and corresponding heterocyclic compounds (chiral and achiral) which have been designed and synthesized so far in our laboratory.

In summary, we have developed a convenient and efficient one-pot three-step route for direct conversion of phenols to anilines using $ClCH_2CONH_2/K_2CO_3$/DMF system with catalytic KI, through Smiles rearrangement as the key step. A range of phenols with electron-withdrawing groups were examined, providing the corresponding anilines in moderate to good yields and demonstrating the potentiality of this transformation towards pharmaceutical and biological aspects.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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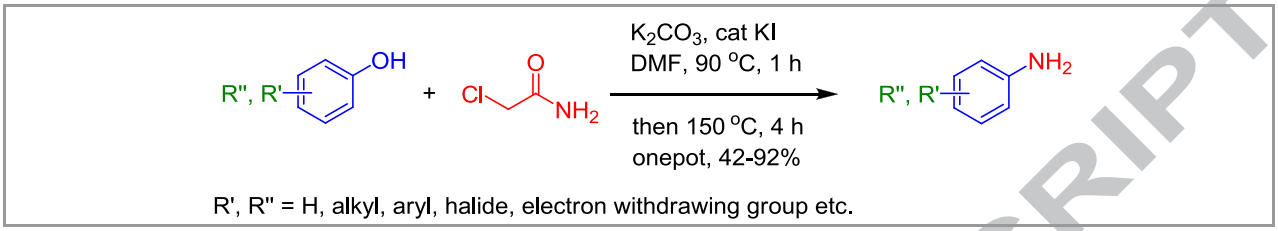
12. Analytical and Spectral data/Physical data of new compounds:
Solvents were dried and purified by conventional methods prior to use. ^{1}H and ^{13}C NMR Spectroscopic data were recorded on an Avance 400 MHz spectrometer in $CDCl_3$ solution using trimethylsilane as an internal standard. Gas chromatography-mass spectrometric (GC-MS) analyses were carried out with a Hewlett-Packard 5890-5970 system. Silica gel (60–120 mesh) was used for flash column chromatography. *5-Chloroquinolin-8-amine (**3i**)*: Brown solid; mp 87.5-88.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (dd, *J* = 4.0 ,1.6 Hz, 1H), 8.46 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.48 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.02 (br s, 2 H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.5, 118.1, 122.1, 126.6, 127.3, 132.9, 138.9, 143.4, 147.8; Mass (EI): m/z = 178 (100%, $[M]^+$). *5,7-Dichloroquinolin-8-amine (**3j**)*: Yellowish solid; mp 122.5-123.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (dd, *J* = 4.4, 1.6 Hz, 1 H), 8.44 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.47-7.50 (m, 2 H), 5.36 (br s, 2 H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.5, 117.7, 122.0, 125.3, 127.6, 133.0, 138.6, 140.2, 148.5; Mass (EI): m/z = 212 (100%, $[M]^+$). *5,7-Dichloro-2-methylquinolin-8-amine (**3k**):* Yellow solid; mp 133.5-134.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.6 Hz, 1H), 7.40 (s, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 5.30 (s, 2H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.65, 139.5, 138.0, 133.0, 126.4, 123.3, 122.7, 117.7, 113.4, 24.9; Mass (EI): m/z = 226 (100%, $[M]^+$).

Graphical abstract

One-pot Conversion of Phenols to Anilines *via* Smiles Rearrangement



R', R'' = H, alkyl, aryl, halide, electron withdrawing group etc.