Tetrahedron Letters 54 (2013) 5151–5154

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot conversion of phenols to anilines via Smiles rearrangement

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ARTICLE INFO

Article history:
Received 10 May 2013
Revised 30 May 2013
Accepted 6 June 2013
Available online 13 June 2013

Keywords:
Phenol
Aniline
Smiles rearrangement
One-pot synthesis

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 °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 derive aryl sulfonates from phenols that have serious problems with respect to cost, and cannot 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,e] *N*-aryl-2-hdroxypropionamides,[6c] 2-bromo-l-naphthylamine,[6d] 6-amino-1-tetralone,[6f] 4-amino-benzofuran,[6g] and 2,3-dihaloanilines.[6h,i] 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.

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.

Our initial attempts to extend the research toward 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

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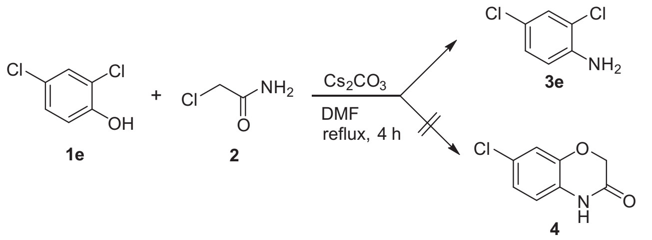
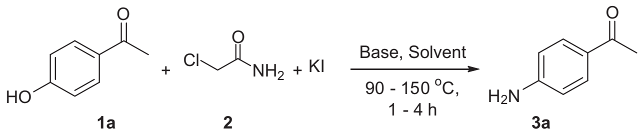
http://dx.doi.org/10.1016/j.tetlet.2013.06.022



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



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**.

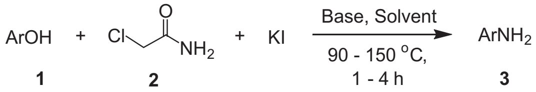
was formed after O-alkylation/Smiles rearrangement sequence. This result encouraged us to explore direct conversion of phenols to anilines as a convenient alternative to the previous methodologies. In addition, DMF can be easily recovered by distillation under reduced pressure and then the residue can be directly purified using silica gel column chromatography, thus avoiding a formal aqueous workup. Various phenols were examined to achieve the corresponding anilines.

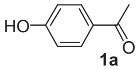
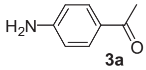
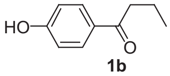
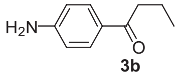
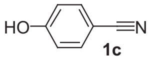
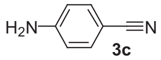
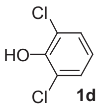
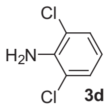
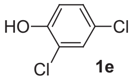
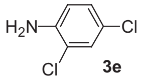
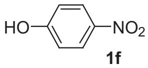
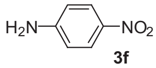
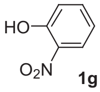
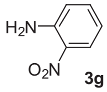
To establish the appropriate reaction conditions, we have chosen 1-(4-hydroxyphenyl)ethanone (**1a**) as a phenol substrate and examined the effects of formal bases and solvents (Scheme 2). At first, we examined the reaction of **1a** (1 equiv) with 2-chloroacetamide (1.2 equiv) in DMF in the presence 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 are presented in Table 2.

This method describes a facile conversion of simple phenols (Table 2, entries 1–3, 6, and 7), chlorophenols (Table 2, entries 4, 5 and 9–11, which even include heterocyclic phenols) their

Table 2
Conversion of various phenols to anilines



Entry	ArOH	Base(s)	Temperature conditions	Products[a]	Yield[b] (%)
1	 **1a**	2.5 equiv K_2CO_3/0.2 equiv KI	90 °C, 2 h then 150 °C, 4 h	 **3a**	75
2	 **1b**	2.5 equiv K_2CO_3/0.2 equiv KI	90 °C,2 h then 150 °C, 4 h	 **3b**	70
3	 **1c**	2.5 equiv $CsCO_3$ or 2.5 equiv K_2CO_3 or 2.5 equiv K_2CO_3/0.2 equiv KI	90 °C, 2 h then 150 °C, 4 h	 **3c**	60[c] 69[d] 84
4	 **1d**	2.5 equiv $CsCO_3$ or 2.5 equiv K_2CO_3/0.2 equiv KI	90 °C, 2 h then 150 °C, 4 h	 **3d**	38[c] 65
5	 **1e**	2.5 equiv K_2CO_3/0.2 equiv KI	90 °C, 2 h then 150 °C, 4 h	 **3e**	62
6	 **1f**	2.5 equiv $CsCO_3$ or 2.5 equiv K_2CO_3/0.2 equiv KI	90 °C, 2 h then 150 °C, 4 h	 **3f**	44[c] 78
7	 **1g**	2.5 equiv $CsCO_3$ or 2.5 equiv K_2CO_3/0.2 equiv KI	90 °C, 2 h then 150 °C, 4 h	 **3g**	50[c] 92