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A Novel Method for the *t*-Butylation of Aromatic Amines

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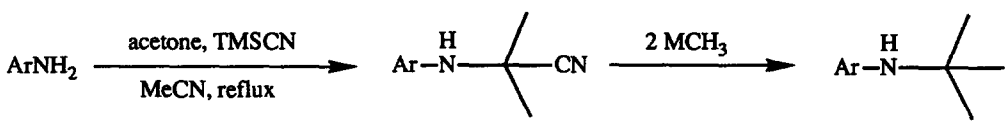
Abstract: A new method for the synthesis of *t*-butylamines from amines in two steps via α-aminonitriles, and its application to various arylamines is discussed.

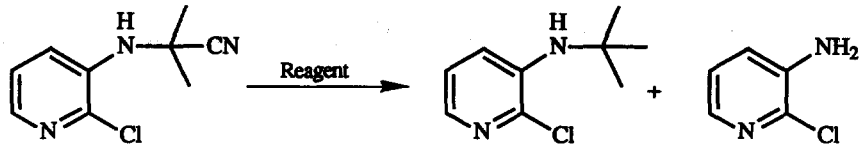
The efficient and mild preparation of *t*-butylamines from primary amine precursors is a transformation of significant interest to medicinal chemists involved in structure-activity relationship studies as well as those investigating the reactivity of highly hindered bases (eg. lithium di-*t*-butylamine). However, the formation of *t*-butylamines from amines has been met with difficulty. Harsh reaction conditions, multiple steps and/or low yields are often encountered. For example, the direct condensation of amines with isobutylene to afford *t*-butylamines has been reported.[1] Unfortunately, this reaction requires very high temperatures (300°C) making it unsuitable for most complex systems. Also, Yamamato has reported the synthesis of *t*-butylamines from primary alkyl and aryl amines in one step via N-alkylation with *t*-Bu_2CuLi in yields of 15-46%.[2] Other oftentimes higher yielding routes to *t*-butylamines from amines require three or more steps. For example, Corey has synthesized di-*t*-alkylamines in three steps via nitroso and hydroxylamino intermediates, in good yields.[3] In addition, Schwartz has recently demonstrated a three step synthesis of *t*-butylamines from dialkyl hydroxylamines via ketonitrones in yields of 60-80%.[4] Recently, we have developed a novel method for the synthesis of *t*-butylamines in good yields from primary aromatic amines in two steps via readily obtainable α-aminonitriles (**Scheme 1**).



Scheme 1.

First the arylamine of interest is converted to the corresponding α-aminonitrile in high yields by treatment with TMSCN and acetone.[5] It has been shown that α-aminonitriles react with a variety of carbon nucleophiles to give products arising either from substitution of the nitrile moiety or 1,2-addition to it.[6] We sought to optimize the substitution pathway by delivering an appropriate methyl nucleophile, such as MeLi, to afford the *t*-butylated product. The initial substrate of interest was the pyridyl amine **1** since we required the *t*-butylated material as a synthetic intermediate. Treatment of **1** with excess MeLi (4 equiv.) in THF at -78° C and warming to room temperature afforded the desired *t*-butylamine **2** in moderate yields (30-50%). As a result of this

promising experiment the reaction conditions were varied and different organometallic reagents were explored in order to optimize this method. The results of these experiments are summarized in **Table 1.**

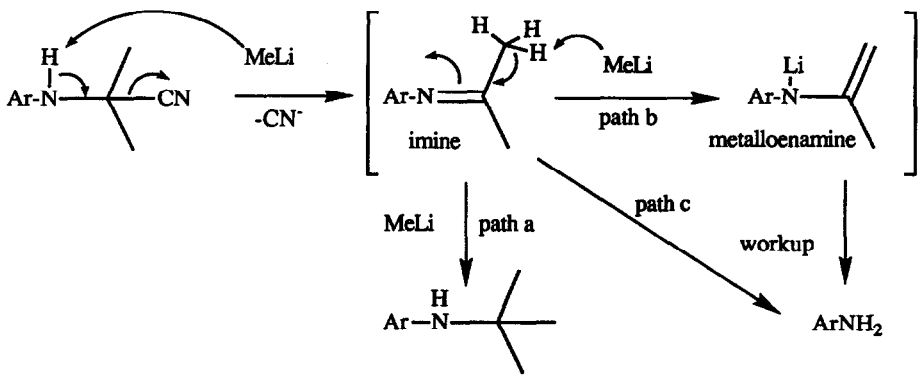


1 **2** **3**

Table 1. Alkylation of **1** Under Varying Reaction Conditions.

Reagent	Solvent	Temp. (°C)	Yield **2**	Yield **3**
MeLi (4 eq.)	THF	-78 - RT	30-50%	45-61%
Me_2CuLi (4 eq.)	Et_2O	-78 - RT	0%	major
MeMgBr (4 eq.)	THF	-78 - RT	0%	major
MeLi (1 eq.) then $MeCeCl_2$(1 eq.)	THF	-78 - RT	36%	52%
$MeCeCl_2$ (4 eq.)	THF	-78 - RT	58%	21%
MeLi (10 eq.)	Toluene	-78 - RT	64%	15%

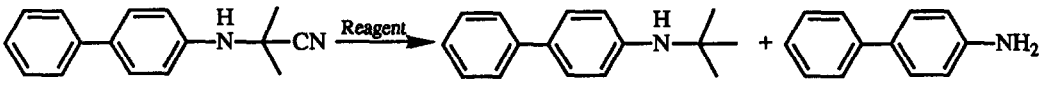
During this study a significant amount of the N-dealkylated arylamine **3** was isolated in addition to the desired product. The formation of **3** can be rationalized by examining the proposed mechanism of the reaction. Presumably, the first equivalent of nucleophile will deprotonate the amine with subsequent elimination of CN^- (**Scheme 2**). Subsequently, another equivalent of nucleophile can either add to the imine to afford the desired product (path a), or deprotonate the imine to give the metalloenamine (path b). Path b is a dead end since the metalloenamine cannot revert back to the imine under these reaction conditions. Thus, it will hydrolyze during the workup to give the free arylamine. Alternately, the free arylamine may simply arise from the hydrolysis of unreacted imine during workup (path c).



Scheme 2.

In an attempt to prevent metalloenamine formation the organocerium reagent ($MeCeCl_2$) was used. Organocerium reagents have been shown to be much less basic than their alkyllithium counterparts.[7-9] Thus, the deprotonation of the methyl group leading to the metalloenamine will be less likely with this reagent. Indeed, employment of $MeCeCl_2$ in THF did lead to higher yields of the desired product **2** (58%).

In another attempt to avoid the formation of the arylamine **3**, the reaction was conducted in less polar solvents. It has been shown that metalloenamines and enamines in general are stabilized by more polar solvents such as THF, and the imine form is more abundant in nonpolar solvents such as benzene or toluene.[10-12] Thus, the reaction was carried out on **1** in toluene using excess MeLi. Consistent yields of >60% were obtained. These higher yields were also accompanied by a decrease in the amount of dealkylated arylamine isolated. Therefore, it appears that metalloenamine formation may be one reason for the isolation of the dealkylated arylamine from THF. Similar results were observed for the biphenyl derivative **4** (**Table 2**). Once again, MeLi in nonpolar solvents such as benzene or toluene provided the best results. Isolated yields of >60% of the *t*-butylated amine **5** were consistently obtained. Other organometallic reagents and/or solvent systems lead to drastic reductions in yields.

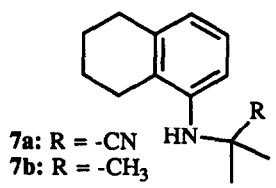


4 **5** **6**

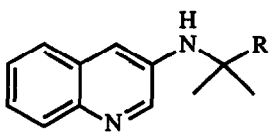
Table 2. Alkylation of **4** Under Varying Reaction Conditions.

Reagent	Solvent	Temp. (°C)	Yield **5**	Yield **6**
MeLi (4 eq.)	THF	-78 - RT	21%	61%
MeMgBr (4 eq.)	THF	0 - 50	< 5%	major
$MeCeCl_2$ (4 eq.)	THF	-78 - RT	45%	30%
Me_2TiCl_2 (4 eq.)	CH_2Cl_2	-40 - RT	0%	>80%
MeLi (4 eq.)	Toluene	-78 - RT	major	minor
MeMgBr (4 eq.)	Toluene	-10 - RT	minor	major
MeLi (10 eq.)	Toluene	-10 - 50	63%	30%
MeLi (10 eq.)	Benzene	10 - 50	>60%	20%

We also studied the α-aminonitriles **7a** and **8a**. Both **7a** and **8a** were treated with excess MeLi in toluene. As expected, **7a** yielded the desired *t*-butylamine **7b** in yields of >50%. The quinoline derivative **8a** also reacted to give the *t*-butylamine **8b**, however a side reaction involving nucleophilic addition of MeLi to the quinoline ring also occurred. This problem could be minimized by holding the temperature of the reaction below -20° C in which case a 40% yield of **8b** was obtained.



7a: R = -CN
7b: R = $-CH_3$



8a: R = -CN
8b: R = $-CH_3$

In conclusion, this method provides a quick and efficient route to *t*-butylamines from primary arylamines via α-aminonitriles. Both the formation of the α-aminonitriles and subsequent reaction with MeLi to afford *t*-butylamines can be accomplished in good overall yields. Further applications of this reaction are under investigation.

General Procedures: α-Aminonitrile synthesis: A solution of the arylamine (1 eq.), acetone (2 eq.), and $ZnCl_2$[13] (0.2 eq.) in CH_3CN is cooled in an ice bath under N_2. Then TMSCN (2 eq.) is introduced and the reaction is heated to reflux. Starting material consumption and product appearance is monitored by TLC.[14] The reaction is worked up in the usual way and the desired α-aminonitrile is crystallized or purified by column chromatography. The α-aminonitriles **1**, **4**, **7a** and **8a** were obtained in yields of 95%, 94%, 82%, and 89%, respectively.

t-Butylamine synthesis: MeLi (1.4 M in Et_2O, 4-10 eq.) is introduced via syringe to dry toluene at -78° C and stirred under N_2. Then a cooled solution of the α-aminonitrile in toluene is added to the MeLi via cannula. The reaction is stirred at -78° C for 30 minutes and then allowed to slowly warm to room temperature where it is stirred for 8 hours.[15] The reaction is then quenched and worked up in the usual way. Purification by column chromatography affords clean *t*-butylamine.

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9. The $MeCeCl_2$ was generated as described by both Imamoto[7] and Denmark.[8] Similar results were observed in either case.
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13. The $ZnCl_2$ must be dried by fusing in a crucible before use.
14. Total reflux times may vary from 4-24 hours.
15. The reaction should be followed by TLC from the outset since the temperature at which the product forms can vary. Also, in some cases heating the reaction slightly (50° C) for 4-5 hours can help the rate of addition to the imine. However, care must be taken because in some systems (i.e. quinoline) heating will result in methylation of the aromatic ring.

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