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ALKYLATION OF 2-AZAALLYL ANIONS; A VERSATILE PRIMARY AMINE SYNTHESIS

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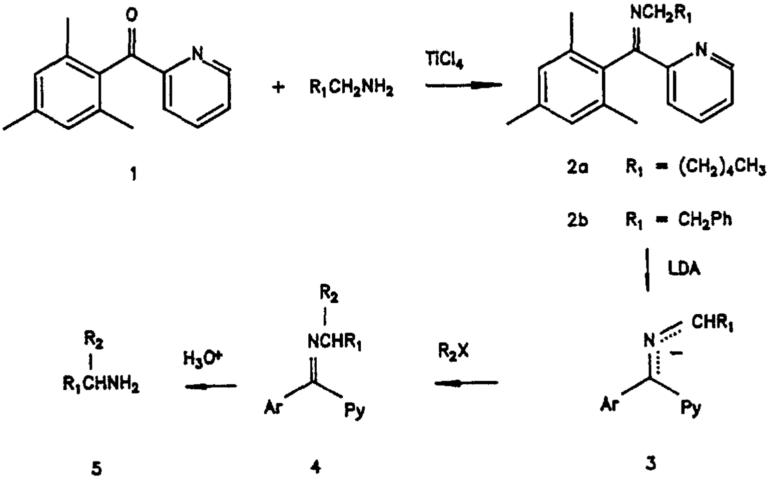
Abstract: Imines from primary amines and mesityl 2-pyridyl ketone react with LDA followed by treatment with an alkyl halide and hydrolysis to give the original amine alkylated at the alpha-position.

Since amines are an important class of organic compounds, there continues to be considerable effort devoted to the development of new methods for their synthesis. A number of methods employing synthetic equivalents of α-amino carbanions have been reported recently[1-3]. Perhaps the method of widest scope for primary amines employs α-metalated isocyanides[2]. The major limitation of this method is the difficulty encountered in metalating alkyl isocyanides whose parent hydrocarbons are less acidic than methane. Another potentially useful method employs 2-azaallyl anions[3] as the α-amino anion synthetic equivalent. This method currently suffers from the same difficulty in forming the anion as the isocyanide method. Furthermore, the 2-azaallyl anion offers two nucleophilic sites and alkylation often occurs at the undesired one. We report here the use of imine **2** to circumvent these problems. In this case, the pyridine ring helps stabilize anion **3**, while the ortho-methyl groups of the mesityl ring direct the alkylation to the desired site.



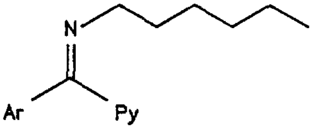
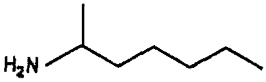
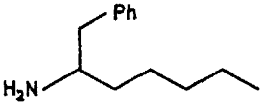
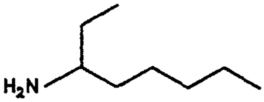
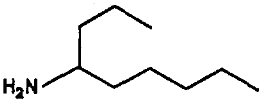
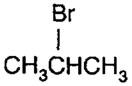
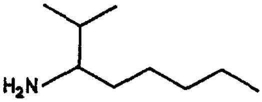
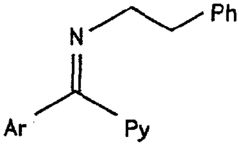
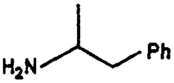
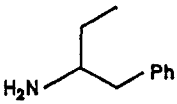
Because of the steric hindrance present in ketone **1**, many common methods for the preparation of imines failed in this case. However, imines **2a** and **2b**[4] could be prepared in good yield by condensation of ketone **1**[5] and the appropriate amine, in the presence of $TiCl_4$[6]. Either of these imines could be deprotonated with LDA in THF to give a deeply maroon-colored solution of the 2-azaallyl anion, **3**. Addition of an alkyl halide caused the slow discharge of the color of the anion. After the color of the anion had completely faded (see Table I for reaction times and conditions), the reaction was quenched with water. Workup of this solution, followed by removal of the solvent and excess alkylating agent at reduced pressure, produced crude alkylated imine, **4**. The NMR spectra of these "crude" alkylated imines were remarkably clean. No starting imine could be detected and the yield of **4** was quantitative. Therefore, the alkylated imines were hydrolyzed without further purification. The only exception to this procedure was the reaction with 2-bromopropane. In this case, **4** (R_1 = hexyl; R_2 = isopropyl) was separated from unreacted starting material in 87% yield by flash chromatography.

As might be expected based upon consideration of steric effects and the difficulty encountered in the preparation of 2, hydrolysis of the alkylated imines was also difficult. Demasking to produce the alkylated amines, **5**, required treatment of **4** with concentrated HCl. The various amines that were prepared and isolated as their benzamide derivatives are shown in Table I. The yields reported in the table are isolated yields of benzamides, starting from imine **2a** or **2b**. Since the alkylation yields were quantitative in most cases, these yields reflect primarily the losses that occur in the hydrolysis step.

From examination of Table I it can be seen that a variety of primary alkyl halides can be used in this reaction. In cases where elimination might compete, high yields can still be obtained by the use of excess base and alkyl halide. Using this strategy, a good yield can be obtained even with a secondary alkyl halide. Although only two different imines were alkylated in this study, the reaction should be fairly general as long as the alkylation site is not sterically hindered. The only drawback to this method is the harsh conditions that are currently required for the hydrolysis of imine **4** to amine **5**. The method should, however, prove useful for the synthesis of primary amines that lack acid sensitive functionality.

Preparation of Imines 2[7]. $TiCl_4$ (90 mmol) in 10 mL of toluene was added dropwise to a solution of 40 mmol of ketone 1 and 80 mmol of the amine in 50 mL of toluene. After refluxing for 12 h, the solution was poured into 200 mL of 10% NaOH solution and worked up in the usual manner. Imine **2a** was isolated in

TABLE I

IMINE	ALKYL HALIDE	RXN TIME	RXN TEMP	AMINE (YIELD)[a]
 **2a**	CH_3I	12 h	RT	 (65)
2a	$PhCH_2Br$	12 h	RT	 (68)
2a	CH_3CH_2Br	48 h	55°C	 (60)
2a	$CH_3CH_2CH_2Br$	48 h	55°C	 (61)
2a	 $CH_3\overset{\overset{Br}{\vert}}{C}HCH_3$	48 h	65°C	 (50)
 **2b**	CH_3I	12 h	RT	 (63)
2b	CH_3CH_2Br	12 h	RT	 (65)

[a] Isolated yields of benzamide derivatives.

80% yield, bp 165° at 0.3 mm. Imine **2b** could not be distilled and was used without further purification.

Alkylation of Imines 2[7]. A solution of 1.5 mmol of imine **2** in 2 mL of dry THF was added to LDA (3.0 mmol for **2a** or 1.8 mmol for **2b**) in 5 mL of dry THF. This solution was stirred for 5 min and then 12 mmol of alkyl halide was added. After the reaction had proceeded as described in Table I, 10 mL of water was added and the reaction was worked up in the usual fashion to give imine 4. This imine was hydrolyzed without further purification.

Hydrolysis of Imines 4. The imine and 10 mL of con HCl were heated to reflux for 2-3 days (the progress of the reaction was followed by TLC). The solution was made basic with NaOH and steam distilled. The distillate was added to 10 mL of 10% NaOH solution containing 1 mL of benzoyl chloride. The benzamides were isolated by extraction and recrystallized from benzene/hexane.

References and Notes

1. For reviews and leading references see: D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 15; P. Beak, D.B. Reitz, *Chem. Rev.* **1978**, *78*, 275; P. Beak, W.J. Zajdel, D.B. Reitz, *Chem. Rev.* **1984**, *84*, 471; A.I. Meyers, P.D. Edwards, W.F. Reiker, T.R. Bailey, *J. Am. Chem. Soc.* **1984**, *106*, 3270; W. Lubosch, D. Seebach, *Helv. Chim. Acta* **1980**, *63*, 102.
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4. All compounds gave IR and proton NMR spectra that were consistent with their assigned structures. All new compounds gave satisfactory combustion analyses, except alkylated imines **4**, which were hydrolyzed without purification. Amines **5** were characterized as their benzamide derivatives.
5. Ketone **1** (mp 66.5-67.5°) was prepared by reaction of mesityl Grignard reagent with 2-pyridinecarboxaldehyde followed by oxidation with CrO_3-pyridine complex in 74% overall yield.
6. H. Weingarten, J.P. Chupp, W.A. White *J. Org. Chem.* **1967**, *32*, 3246.
7. Reactions were performed under an atmosphere of dry nitrogen.

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