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A VARIANT OF THE BRUYLANTS REACTION. SYNTHESIS OF 4-HETEROARYL-4-ANILINOPIPERIDINES.

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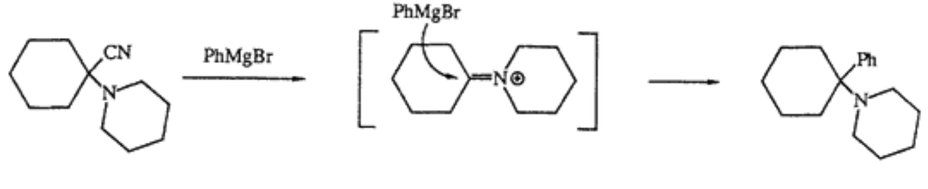
Abstract: Imines can be generated in situ from α-aminonitriles and efficiently trapped by a variety of lithiated heterocycles. This variation of the Bruylants reaction has proven to be a general method for the synthesis of α-heteroaryl secondary amines.

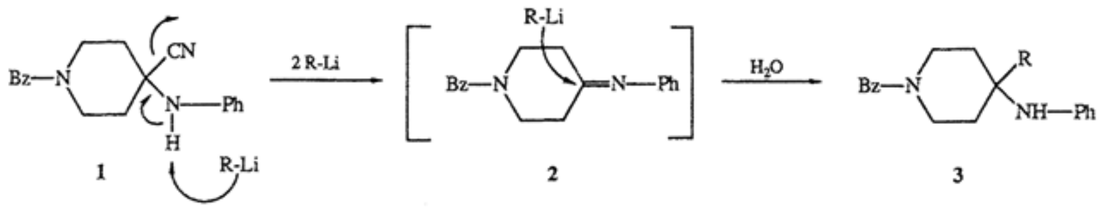
The versatility of α-aminonitriles as intermediates in the preparation of highly substituted amines is well documented in the literature[1]. An important example of the synthetic utility of α-aminonitriles is the apparent displacement of the cyano group of an α-aminonitrile by Grignard reagents in the Bruylants reaction[2].



In this sequence of events the tertiary α-aminonitrile serves as the source of a tertiary iminium salt which is generated in situ via elimination of the cyano group. The resultant iminium salt then undergoes Grignard addition to afford the desired substituted amine. Because of their stability and solubility in common organic solvents α-aminonitriles are a synthetically useful source of tertiary iminium salts. We have demonstrated that secondary α-aminonitriles can serve as a convenient precursor to imines or Schiff bases via elimination of the cyano group in a manner analogous to that in the Bruylants reaction.

Herein, we report the synthesis of a series of 4-heteroaryl-4-anilinopiperidines utilizing this variant of the Bruylants reaction. Attempts to synthesize α-heteroaryl secondary amines via nucleophilic attack of pre-formed and isolated Schiff bases by metalated heterocycles resulted in poor yields, predominantly due to proton transfer. This problem was overcome by generating the appropriate imines in situ from the corresponding secondary

α-aminonitriles 1. The imines 2 thus formed were efficiently trapped by lithiated heterocycles usually yielding the desired products 3 in high yield.

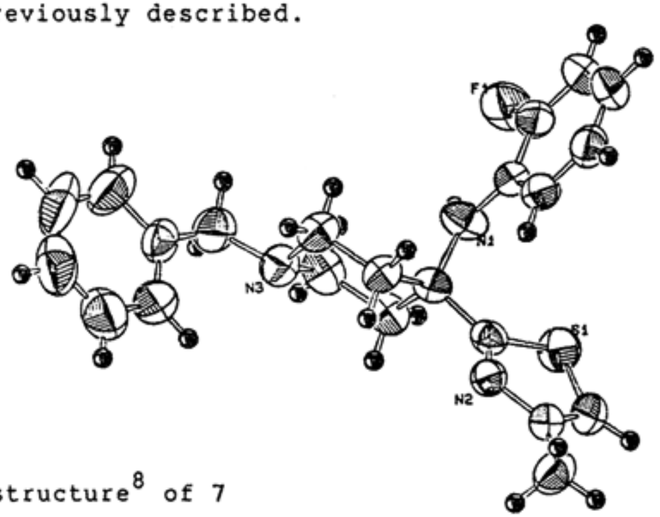


R= Heteroaryl

Table I depicts the efficiency of this general synthetic method for the construction of a variety of 4-heteroaryl-4-anilinopiperidines. A typical procedure is described below.

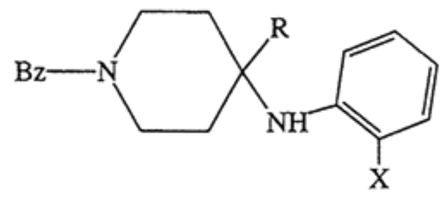
4-Methylthiazole (2.30 gm, 23 mmol) was added via syringe to a cold (-78 °C) solution of butyllithium (23 mmol, 23 ml 1M butyllithium in hexanes) in 60 mls of tetrahydrofuran under argon. The solution rapidly turned deep orange and became turbid. The solution was stirred at -78 °C for 10 min. followed by rapid addition of a solution of 1-benzyl-4-cyano-4-anilinopiperidine[3] (3.16 gm, 10.8 mmol) in tetrahydrofuran (30 ml) via cannula. The reaction was stirred for 0.5 H while warming to 0 °C and was quenched with H_2O (10 ml). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography[4] to give an amber oil (R_f= 0.20, 30% ethyl acetate in hexane) which was crystallized from hot hexane to give 1-benzyl-4-(4-methylthiazol-2-yl)-4-anilinopiperidine 6 as tan crystals (3.41 gm, 87%).

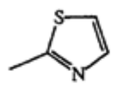
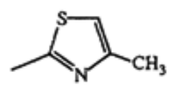
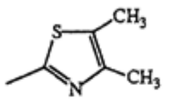
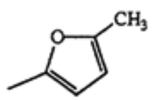
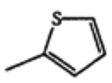
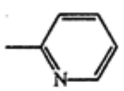
Thiazole and 4,5-dimethylthiazole were metalated with butyllithium as above. 2-Lithio-5-methylfuran[5], 2-lithiothiophene[6] and 2-lithiopyridine[7] were prepared as previously described.



X-Ray structure[8] of 7

Table I: 1-BENZYL-4-HETEROARYL-4-ANILINOPIPERIDINES



Entry	R	X	mp (°C)	% yield[a]
4		H	146	89
5		F	125	92
6		H	119	87
7		F	101	98
8		H	oil	87
9		F	oil	85
10		F	148	57
11		F	oil	20
12		H	108	51
13		F	oil	71

[a] All % yields reported are for chromatographically homogeneous compounds. All new compounds were fully characterized by IR, NMR, MS and gave satisfactory CHN analysis.

It is not clear why nucleophilic attack predominates when α-aminonitriles are used as imine equivalents. Participation of the cyanide ion in the course of the reaction was ruled out. Addition of an equivalent of LiCN to a solution of 2-lithio-4-methylthiazole in tetrahydrofuran at -78 ^{0}C followed by 1-benzyl-4-phenyliminopiperidine[9] did not appear to enhance nucleophilic substitution. The yield of **6** was identical to that observed without LiCN (40%). Therefore, there was no apparent salt effect.

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3. P.A.J. Janssen, U.S. Patent 3,155,670 (1964). 1-Benzyl-4-cyano-4-(2-fluoroanilino)piperidine kindly provided by Dr. B.S. Huang, was prepared in the analogous manner.

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6. H. Gilman and D.A. Shirley, J. Am. Chem. Soc., 1943, 71, 1870.

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8. X-Ray structure provided by Dr. E. Ezell, BOC Group Technical Center.

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