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Short communication

The mechanism of lithiation and nitrile insertion reactions of β-methylazines: evidence from the structure of 3-$C_5H_4NCH{=}C(Ph)N(H)C(Ph){=}NLi \cdot PMDETA$ [1]

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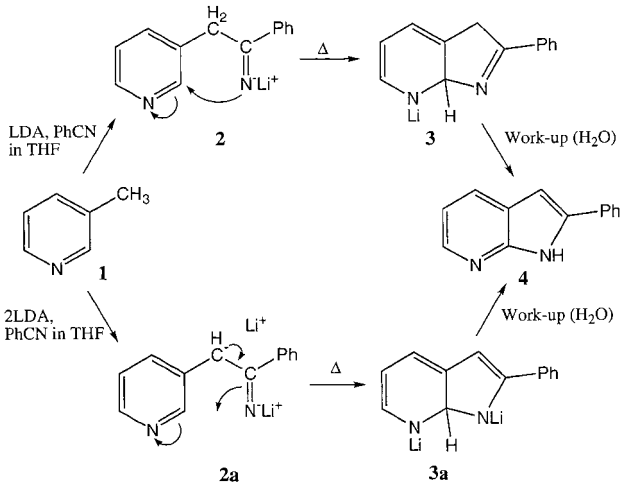
Abstract

A 1:1:1 reaction of 3-methylpyridine, **1**, with LDA and PhCN in the presence of PMDETA gives the title complex **6**, shown by X-ray crystallography to be the first monomeric iminolithium. The isolation of **6**, and of a cyclised product **8** when a 3:10:3 reaction of **1**:LDA:PhCN is carried out, suggest a mechanism for previously published cyclisation reactions of β-methylazines. © 1998 Elsevier Science S.A.

Keywords: Lithium; Reaction mechanisms; Nitriles; X-ray structure

1. Introduction

Several of our recent papers have concerned the isolation and structural characterisation of lithium-containing species present during 'one-pot' organic syntheses involving lithiations [1–5]. In all cases, the originally proposed reaction mechanism/sequence involved the generation of both mono- and di-lithiated organic molecules. However, so far the latter species have proved very elusive. For example, our most recent study [5] examined briefly a versatile protocol whereby β-methylazines (pyridines, quinolines, pyrimidines etc.) undergo lithiation and nitrile insertion, then ring closure [6]. Scheme 1 shows the reaction sequence proposed in the original paper, taking 3-methylpyridine **1** as the precursor. Monolithiation (top equation) and benzonitrile insertion, followed by thermolysis and work-up, give the final organic product **4**. However, yields are only moderate even under forcing conditions: in this specific case, 63% after heating at 100°C for 36 h. Better yields under milder conditions (90% after heating at 40°C for 4 h) are gained when an excess (two-fold or more) of lithiating reagent is used (Scheme 1, bottom equation). Such improvement was attributed [6] to formation of a dilithiated intermediate **2a**.



Scheme 1.

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[1] Dedicated to Professor Ken Wade on the occasion of his 65th birthday and in recognition of his outstanding contributions to Chemistry. R.S. in particular thanks Ken, his erstwhile PhD supervisor, for his strong support and valued friendship over many years.

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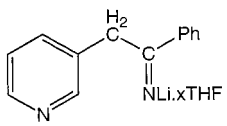
In our preliminary study [5] we could not isolate such a species although dilithiation of the related (but much more acidic) 2-methylpyridine followed by PhCN insertion did give in high yield a dilithiated product: a complicated Li_{12} aggregate containing two types of dianion, viz, $[C_5H_4N \cdot CHC(Ph)N^{2-} \cdot 2Li^+]_2 \cdot [C_5H_4N \cdot CH^-(Li \cdot THF) \cdot C(Ph)N^-Li^+]_4$. Here we describe the results of a more detailed study of the reactions shown in Scheme 1. The major conclusions are: (i) that the monolithium species **2** is not that formulated in Scheme 1 (and below) but rather is probably $C_5H_4N \cdot CH{=}C(Ph)NHLi$, **5**, i.e., the C=C bond apparent in the five-membered ring of the final product **4** is formed at this stage; (ii) that dilithium species **2a** and **3a** are not isolable as solid materials even if they might be present in the reaction solution; and (iii), from (i) and (ii), that product **4** results from cyclisation then work-up of the monolithium species **5** whose efficient production (and, possibly, whose cyclisation) depends upon the presence of excess (two- or more-fold) LDA.



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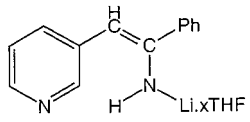

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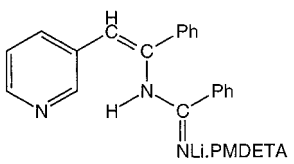
2. Results and discussion

Initially we attempted to synthesise a monolithium complex of type **2** by reacting 3-methylpyridine **1** with one equivalent each of LDA and PhCN in THF as solvent (Scheme 1, top equation). Cooling of the reaction solution over several days failed to afford crystals even after removal of much of the THF. Accordingly, the reaction was repeated in the presence of one equivalent of an alternative Lewis base, PMDETA $[MeN(CH_2CH_2NMe_2)_2]$. Refrigeration of this reaction solution over a week then gave crystals of **6** in reasonable yield (51%). Complex **6** was characterised initially by elemental analyses and by ^1H, ^{13}C NMR spectroscopy. The species has several key and interesting features. Firstly, *two* equivalents of PhCN have been inserted into lithiated **1**, $2\text{-}C_5H_4NCH_2Li$; the implications are that lithiation is slow and/or incomplete and that the nitrile insertion reactions are much faster. Secondly, as shown by NMR spectroscopy, **6** contains a $-CH{=}C(Ph)NH-$ unit rather than a $-CH_2-C(Ph){=}N-$ one, as in **7**. Put another way, while both **6** and **7** can be considered to be iminolithium species of type $Ph(R)C{=}NLi$, in **6** *R* is an alkenylamino-group whereas in **7** it is an imino-group. This suggests that the product of lithiation of **1** followed by insertion of *one* equivalent of PhCN is not **2**, but rather it is **5**. This is significant in that the C=C bond of the pyrrole ring in the final product **4** is formed already in **5**.



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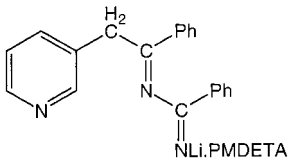

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The identity of **6** was confirmed by X-ray crystallography. The molecular structure (Fig. 1) is monomeric and shows the features apparent from solution NMR spectroscopy. The single Li centre is approximately tetrahedrally coordinated by an imino N[N(1)–Li(1) distance, 1.963(8) Å] and by the three N atoms of a disordered PMDETA ligand [mean of six N–Li distances, 2.124(10) Å]. The central backbone of the molecule consists of a zig-zag-NC(Ph)N(H)C(Ph)C(H)– unit involving as the key atoms N(1)C(1)-N(3)C(14)C(15). Although the bonding within this unit can be represented formally by N(1)=C(1)–N(3)–C(14)=C(15) [see structural formula **6**] it is apparent from the bond lengths that there is considerable delocalisation along the backbone; these lengths are N(1)–C(1) 1.320(5), C(1)–N(3) 1.331(5), N(3)–C(14) 1.381(5) and C(14)–C(15) 1.352(5) Å. The C–N distances can be compared with those found within the pyridyl ring [mean 1.326(6) Å] and the C–C one with those distances found in the two phenyl groups [mean 1.383(7) Å]. The essentially sp^2 and planar natures of the imino carbon atom C(1) and the alkenyl carbon atom C(14) are further confirmed by the summations of the angles around them, 360.0° and 359.3° respectively.

It was noted above that **6** could be considered as an iminolithium complex of type $Ph(R)C{=}NLi \cdot PMDETA$ where *R* is the alkenylamino-group $2\text{-}C_5H_4N \cdot CH{=}C(Ph)N(H)-$. As such it is the first example—albeit a somewhat elaborate one—of a monomeric iminolithium species. In this context, it is pleasing and appropriate to note that the first structurally-characterised iminolithium, the uncomplexed hexamer $(Bu^t_2C{=}NLi)_6$, was reported in 1979 by Shearer et al. [7]. Since then, further hexameric structures have been revealed [8,9] as have pseudo-cubane tetrameric complexes such as $(Ph_2C{=}NLi \cdot Pyr)_4$ and dimeric complexes such as $(Bu^t_2C{=}NLi \cdot HMPA)_2$ [8–11].

In the light of the above results on the monolithiation of **1** and subsequent (double) PhCN insertion, we have examined more closely the course of the supposed dilithiation of **1** (Scheme 1, bottom equation). Treatment of **1** in THF with LDA and then PhCN (3:5:3 equivalents), followed after 1.5 h by five further equiva-

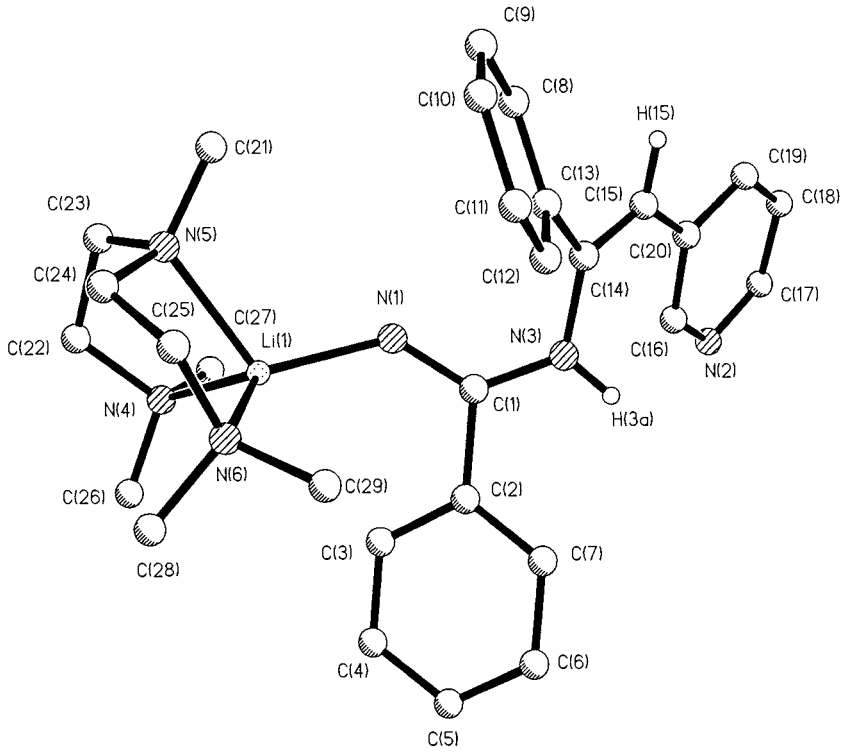
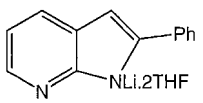


Fig. 1. Molecular structure of **6** [hydrogen atoms other than H(3a) and H(15), and the disorder within the PMDETA molecule, are omitted for clarity].

lents of LDA gives a clear solution. No crystalline material could be isolated from this solution even after prolonged refrigeration. Detailed NMR experiments remain to be done but certainly so far we have no evidence for the formation of a *di*lithiated species such as **2a**. However, heating of this reaction solution at 40°C for 4 h did, after cooling, give a *mono*lithium product, **8**, in 60% yield. Its crystal structure is awaited but its empirical identity has been proved by ^{1}H, ^{13}C NMR spectroscopy. Most importantly, **8** is an obvious immediate forerunner (cf., **3, 3a** in Scheme 1) of the organic product **4**. Indeed, hydrolysis of **8** followed by work-up gives **4** in 90% yield. In reverse, lithiation of **4** by $Bu^{n}Li$ reproduces **8**.



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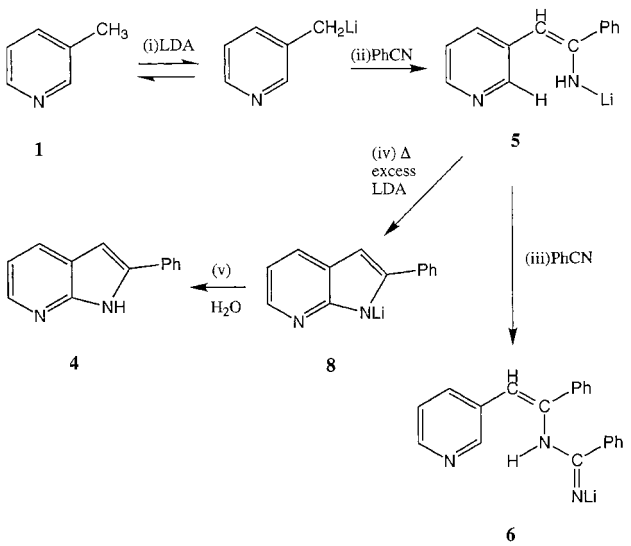
Tying together all these results, our preliminary conclusions are expressed in Scheme 2. The first step [(i)] is clearly the monolithiation of **1**. The product can insert one equivalent of PhCN to give **5** [step (ii)] or, as we have shown, it can insert two PhCN units to give **6** [step (iii)]. Which of these processes dominates will clearly depend on the rate and extent of production of lithiated **1** in step (i). If this species is produced only slowly or incompletely, then in effect PhCN is present in excess and **6** will be the dominant product. Herein, we believe, lies the explanation for the efficacy of using two or more equivalents of LDA in the first stage of these syntheses. The excess of LDA is not there to produce



Scheme 2.

dilithiated species such as **2a** (Scheme 1), for which we can find no evidence. Rather, it ensures the more rapid and/or more extensive production of lithiated **1**. Evidencing this, the ^{1}H NMR spectrum of a 1:1 mixture of **1** and LDA in d_8-THF at 25°C indicates a mixture of **1** and lithiated **1** (ca. 50% of lithiated **1**), whilst a similar spectrum of a 3:5 mixture shows more complete monolithiation of **1** (ca. 75%). Efficient production of lithiated **1** will lead to **5**, not **6**, as the dominant insertion product. The key feature of our precise formulation of **5** is its $-HC=\underset{|}{C}-NH-$ unit which sets it up perfectly for ring closure to give, eventually, the final organic product **4**. Such formulation, and the presence of such a unit, is in part inferred from the structure of **6**. However, further to this inference, we can cite the fact that treatment of 2-methylpyridine with LDA in the presence of TMEDA [$Me_2N(CH_2)_2NMe_2$] and then Bu^tCN affords not 2-$C_5H_4N \cdot CH_2C(Bu^t)=NLi \cdot$ TMEDA but rather 2-$C_5H_4N \cdot CH=C(Bu^t)NHLi \cdot$ TMEDA. [2] The final uncertain and largely unexplored stage is precisely how **5** cyclises on heating to give **8** [step (iv)]. In Scheme 2, we imply that this step formally involves elimination of dihydrogen. However, it is more conceivable that excess LDA still in the system lithiates **5** at the N–H position and that the resulting *geminal* $-NLi_2$ species (or even a *vicinal* one such as **3a)** is the immediate precursor to complex **8**, formed by LiH elimination.

3. Experimental

3.1. Synthesis and characterisation of *6*

3-methylpyridine (0.48 ml, 5 mmol) was added to a chilled solution of LDA ($^iPr_2NLi$ 0.535 g, 5 mmol) in THF (8 ml). The resulting yellow suspension was chilled to −78°C and PhCN (0.51 ml, 5 mmol) was added. The mixture was stirred for 1.5 h at 0°C, resulting in a clear red-brown solution. The THF was removed to produce an orange powder which was recrystallised from PMDETA (0.7 ml, 5 mmol) and toluene (8 ml). Refrigeration for 1 week afforded orange crystals of **6** $(C_5H_4N)CHC(Ph)NHC(Ph)NLi \cdot$ PMDETA. First batch yield 0.60 g (51%). Analysis for **6** $C_{29}H_{39}N_6Li$. Found C72.44, H8.22, N17.72, Li 1.39%; Calc. C72.75, H 8.22, N17.56, Li 1.47%. ^{1}H NMR spectrum (250 MHz, DMSO) alkenyl CH proton δ 5.72 ppm (*s*, integration 1H relative to C_5H_4N and $2\times$Ph resonances). ^{13}C NMR spectrum (400 MHz, DMSO) alkenyl CH carbon resonance at δ 103.7 ppm (H odd by APT scans).

3.2. Crystallographic data for *6*

$C_{29}H_{39}LiN_6$; $M = 478.60$, colourless crystals, dimensions $0.41\times0.34\times0.22$ mm, monoclinic, $P2_1/c$ (No. 14), $a = 10.21(2)$, $b = 15.81(3)$ $c = 17.76(4)$ Å, $\beta = 96.8(2)$; $V = 2849(10)$ Å^3, $D_{calc} = 1.116$ Mg/m^3, $Z = 4$, F(000) = 1032, graphite-monochromated Mo-K_α radiation, $\lambda = 0.71073$ Å, μ(Mo-K_α) = 0.067 mm^{-1}, $T = 153(2)$ K. Data were collected on a Stoe four-circle diffractometer equipped with an Oxford Cryostream crystal cooling apparatus. A total of 6113 reflections (3692 independent, $R_{int} = 0.065$) were collected in the range $7.08 \le \theta \le 22.50°$. Structure solved by direct methods (SHELXTL-PLUS) and refined with all non-hydrogen atoms anisotropic by full-matrix least squares based on F^2 (SHELXL-93); H atoms were included in idealised positions [whilst H(15) on C(15) and H(3a) on N(3) could be located in the difference electron density map their coordinates were not refined freely]. The PMDETA ligand is positionally disordered over two different sites and was refined with partial occupancies and with appropriate restraints to positional and displacement parameters. The final cycle of refinement included 310 parameters with unweighted $R_1 = 0.0714$ on 2694 data with $I > 2\sigma(I)$ and weighed $wR_2 = 0.1939$ on all data. G.o.f. 1.062, weighing scheme $w^{-1} = [\sigma^2(F^2) + (0.0589P)^2 + 3.04P]$ where $P = [F_o^2 + 2F_c^2/3]$. Highest peak in final difference map 0.575 e Å^{-3}. Atomic coordinates, bond lengths and angles, and vibrational parameters have been deposited at the Cambridge Crystallographic Data Centre. This information may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

3.3. Synthesis and characterisation of *8*

3-methylpyridine (3 mmol, 0.3 ml) was added to a solution of LDA (5 mmol). On stirring a yellow suspension resulted. This was chilled to −78°C and PhCN (3 mmol, 0.3 ml) added. The mixture was stirred at 0°C for 1.5 h resulting in a clear red-brown solution. A further portion of LDA solution (5 mmol) was then added and the solution heated for 4 h at 40°C. The resulting red solution was filtered to remove a small amount of fine precipitate. Refrigeration for two days afforded orange crystals of **8**, $C_{21}H_{25}LiN_2O_2$. First batch yield 0.72 g (41%), mp 127–129°C. Analysis found C72.70, H7.30, N8.26, Li1.84%. Calc. C73.21, H7.32, N8.10, Li2.04%. ^{1}H NMR (250 MHz, DMSO) δ 7.96 (dd, 2H, Ph), 7.81 (dd, 1H, Pyr), 7.51 (dd, 1H, Pyr), 7.27 (dd, 2H, Ph),

[2] The crystal structure of this complex has been solved; it is a polymer with $(NLi)_2$ rings linked together by TMEDA molecules. S.C. Ball, R.P. Davies, P.R. Raithby, R. Snaith, unpublished observations.

7.07 (t, 1H, Ph), 6.54 (s, 1H), 6.48 (dd, 1H, Pyr), 3.60 (m, 8H, THF), 1.77 (m, 8H, THF). ^{13}C NMR (100.6 MHz, DMSO) 159.3 (H even), 149.1 (H even), 140.2 (H even), 137.5 (H odd), 127.7 (H odd), 125.2 (H odd), 124.6(H odd), 124.4 (H even), 123.3 (H odd), 110.0 (H odd), 91.7 (H odd), 66.9 (H even), 25.1 (H even).

4 was prepared via hydrolysis of a solution of **8**, followed by extraction and purification as described in Ref. [6]. mp 209–210°C, ^{1}H NMR (250 MHz DMSO), δ 12.16 (*s*, 1H, NH), 8.20 (dd, 1H), 7.95 (m, 3H), 7.47 (dd, 2H), 7.39 (t, 1H), 7.09 (dd, 1H), 6.94 (s, 1H). Reaction of **4** with one equivalent of ^{n}BuLi in a 1:1 THF:hexane solvent afforded crystals of **8** in moderate yield.

Acknowledgements

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