# The Role of Lithium Amides as Reducing Agents in a Novel Pathway to 3,6-Diarylpyridazines by Ring Transformations of 3,6-Diaryl-*s*-tetrazines

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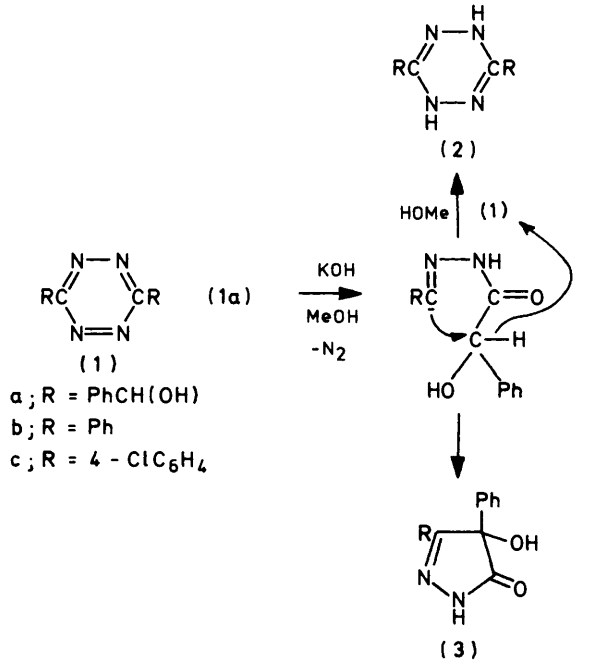
3,6-Diaryl-*s*-tetrazines undergo two competing reactions when treated with lithium amides. The first, direct nucleophilic attack and addition of lithium amide to the tetrazine, appears to be predominant when a less hindered amide is used, and moderate quantities of tetrazine are then regenerated on quenching. The competing reaction, which is seen more clearly with a bulkier amide such as lithium di-isopropylamide, involves reduction of tetrazine to a dihydro derivative with concomitant formation of imine from the amide : this imine is then attacked by further amide and gives rise to a charged intermediate which reacts with more tetrazine to form a pyridazine.

We recently reported the ability of *s*-tetrazines to abstract hydride ions from anionic species under basic conditions,[1,2] *e.g.* in the formation of the 4-arylpyrazol-5-one (3a) from 3,6-bis-(α-hydroxybenzyl)-*s*-tetrazine (1a) (Scheme 1). We now report ring transformations of 3,6-diaryl-*s*-tetrazines (1; R = Ar) into pyridazines (11) where again the ability of *s*-tetrazines to abstract hydride ions from an anionic species is a key step.

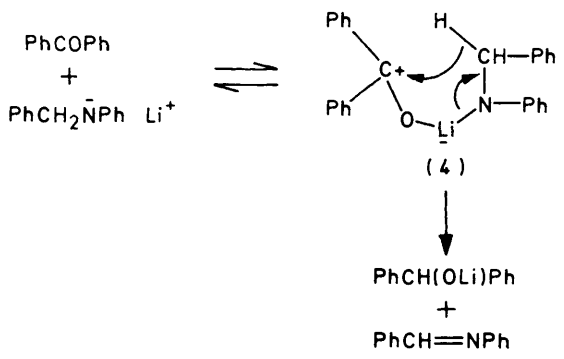
When 3,6-diphenyl-*s*-tetrazine (1b) was treated with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) under dry nitrogen, the principal products isolated were 4-methyl-3,6-diphenylpyridazine (11a) and 1,4-dihydro-3,6-diphenyl-*s*-tetrazine (2b). In addition, a substantial quantity of starting tetrazine (1b) was recovered. The following explanation is proposed for these results. Although the normal mode of action of LDA is as a hindered base [3] its role as a reducing agent for carbonyl compounds has been reported,[4,5] as have similar reductions using other lithium amides.[6] Although there is some evidence that these reductions proceed *via* an electron-transfer mechanism,[7] Wittig [8] specifically excluded this route for the reduction of benzophenone with lithium *N*-benzylanilide and presented evidence that a complex (4) was formed which allowed transfer of a hydride ion *via* a cyclic transition state (Scheme 2). On the basis that tetrazines (1), like carbonyl compounds, readily appear to accept a hydride ion, the dihydrotetrazine (2b) in our reaction would be produced by reduction of the tetrazine (1b) with LDA (Scheme 3), the metallated intermediate (5) forming the dihydrotetrazine (2b) during quenching. The imine intermediate (6), formed by oxidation of LDA, would be susceptible to attack by a second molecule of LDA acting this time in its more usual role as a base (Scheme 4). This reaction step (6) ⟶ (7) finds support in the analogous use of LDA by Wittig,[9] who used metallated Schiff's bases ($RN{=}CHCH_3$ + LDA ⟶ $RN{=}CHCH_2^-\ Li^+$) to prepare aldol-type products from ketones.

The final step in the formation of the pyridazine (11a) could then occur by either of two routes corresponding to the two hybrid forms of the deprotonated imine (7a or b). *s*-Tetrazines appear to be susceptible to nucleophilic attack at a ring carbon atom [1,2] and hence the species (7a) could attack a molecule of the tetrazine (1b or c) with elimination of molecular nitrogen to form the ion (8). Ring closure would then produce a dihydropyridazine (10) which would aromatise by loss of isopropylamine (or its lithium amide) (Scheme 4). Alternatively, this step could occur *via* a [4 + 2] cycloaddition of the enamine (7b). Related Diels–Alder additions of *s*-tetrazines with dienophiles containing an uncharged double bond are widely reported (see ref. 10 and references therein). Indeed,

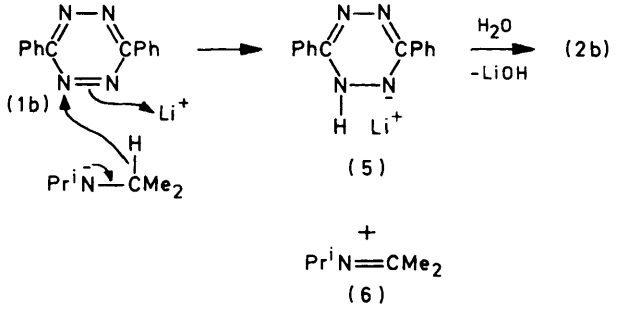



**Scheme 1.**

Sauer [11] prepared 3,4,6-triphenylpyridazine from 3,6-diphenyl-*s*-tetrazine by reaction with enamines. Bridged intermediates, related to compound (9), readily lose nitrogen and give 4,5-dihydropyridazines (10) which then aromatise provided C-4 or C-5 carries a good leaving group. Since Sauer's Diels–Alder reaction required prolonged heating in toluene to bring it about and our reaction took place within an hour at room temperature in THF it is possible that the ionic pathway (path *a*, Scheme 4) is the more likely. However, the cycloaddition mechanism (path *b*) cannot be ruled out since such reactions are known to be promoted by electron-releasing groups on the dienophiles, and the enamine-like amide (7b) having a negative charge may be sufficiently more reactive to bring about the condensation (7b) ⟶ (9) under milder conditions. In either case isopropylamine would arise as a by-product (Scheme 4) and this was conclusively shown by n.m.r. spectroscopy. 3,6-Bis-(4-chlorophenyl)-4-methylpyridazine (11b) was also prepared by the action of LDA on the corresponding tetrazine (1c).



Scheme 2.

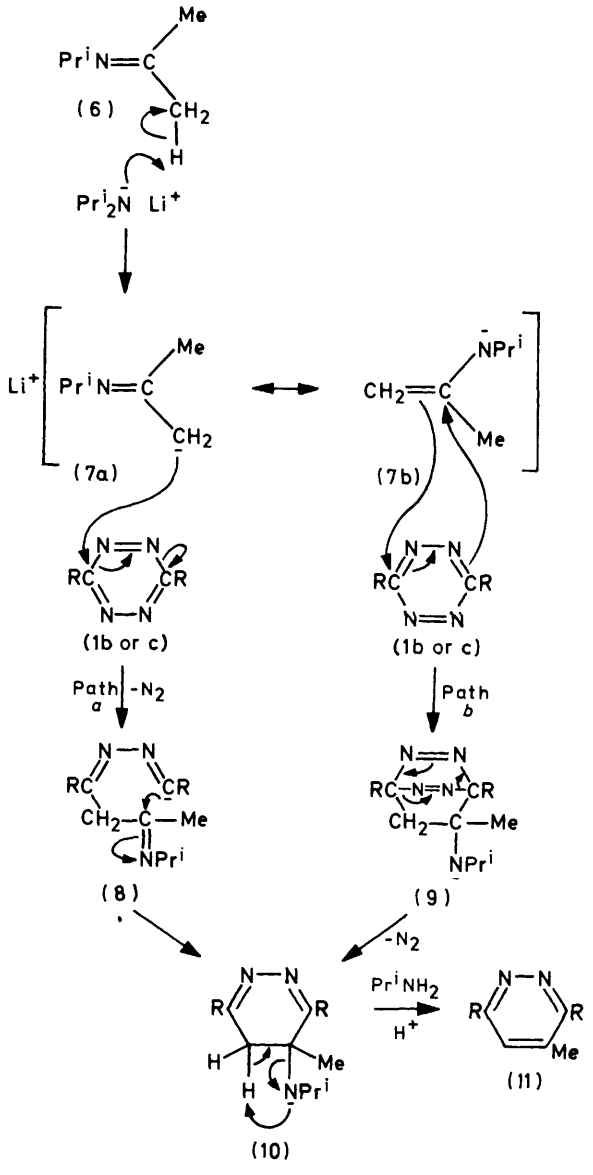


Scheme 3.

*As yields of* the pyridazines (11a, b) were not high, and yet during the reaction the intense red colour of the tetrazines (1b, c) was discharged, we propose that a competing reaction takes place, *viz.* attack of LDA on the tetrazine (1b or c) to give an adduct (12; R′ = Pr$^i$) (Scheme 5). Support for this comes in the recovery of moderate quantities of a red tetrazine (1b or c) and di-isopropylamine immediately on quenching and work-up. Further support lies in the observation by Creary and his co-workers [5] that reduction of ketones with LDA is to some extent inhibited by the formation of $R_2C(O^-)$-$NPr^i_2$ by nucleophilic attack of amide ion on the carbonyl group.

When the tetrazine (1b) was treated with lithium diethylamide under similar conditions to the above only a small amount of the expected 3,6-diphenylpyridazine (13), along with dihydrotetrazine (2b), was isolated, most of the tetrazine (1b), whose red colour was discharged during the reaction, being recovered on quenching. This adds weight to our proposal stated above regarding the competitive formation of an adduct by nucleophilic attack of the amide ion on the tetrazine ring. The diethylamide ion, being more nucleophilic than the bulkier di-isopropylamide ion, could be expected to form an adduct (12; R = Ph, R′ = Et) in preference to undergoing oxidation by loss of hydride ion.

For the purpose of identification, the pyridazines (11a) and (13) were prepared by the method of Sauer [11] by the action of the tetrazine (1b) with propenyl propyl ether and ethyl vinyl ether, respectively.



For (8)–(11) a; R = Ph
b; R = 4-ClC$_6$H$_4$
For (1) see Scheme 1

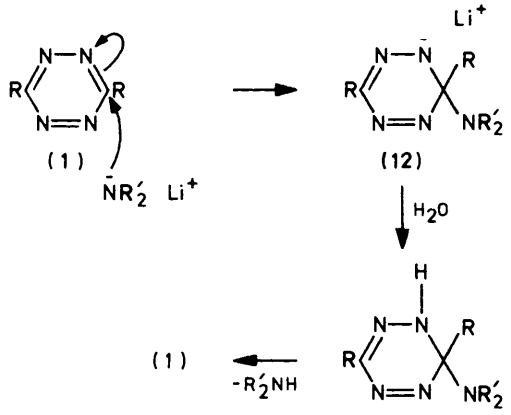
Scheme 4.

## Experimental

M.p.s are uncorrected. N.m.r. spectra were run on a Varian EM 360 (60 MHz) instrument.

*Preparation of Imidate Salts.*—Standard Pinner syntheses [12,13] were used to prepare ethyl benzimidate hydrochloride, m.p. 124—127 °C (decomp.) (lit.,[14] 128—129 °C) and ethyl 4-chlorobenzimidate hydrochloride, m.p. 177—178 °C (decomp.) which corresponds to the literature [15] m.p. of 4-chlorobenzamide (179 °C) (see ref. 13).

*Preparation of the Tetrazines* (1b, c).—Ethyl 4-chlorobenzimidate hydrochloride (8.3 g) was added in portions to a stirred solution of hydrazine hydrate (11.5 g) in ethanol (19 ml) cooled in an ice-bath. The mixture was stirred for a further 4 h, and then the solid product was filtered off and washed with water. The crude dihydrotetrazine (2c) was mixed with a stirred solution of sodium nitrite (3.9 g) in water (20 ml) at 0 °C and glacial acetic acid (23 ml) was added dropwise. The mixture was stirred at 0 °C for a further 2 h and then more sodium nitrite (0.7 g) and glacial acetic acid (5 ml) were added. The mixture was stirred at room temperature for a further 2 h and the crude product was filtered off and triturated with hot dimethylformamide to remove a white impurity. Crystallization from toluene then gave tetrazine (1c) (0.4 g) which softens at 300 °C and sublimes thereafter (lit.,[16] m.p. 315 °C).



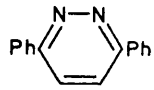
Scheme 5. R′ = Pr$^{i}$ or Et (see text)

The tetrazine (1b), prepared similarly from ethyl benzimidate hydrochloride, had m.p. 196—198 °C (from benzene) (lit.,[17] 198 °C).

*Preparation of Lithium Amides.*—n-Butyl-lithium (1.6M; 0.002 mol) was added to a stirred solution of the secondary amine (0.002 mol) in dry THF (10 ml) at −10 °C under dry nitrogen. The mixture was stirred at this temperature for 10 min and then the temperature was reduced to −70 °C.

*Action of LDA on* 3,6-*Diphenyl*-s-*tetrazine* (1b).—Under dry nitrogen, a solution of LDA (0.002 mol) prepared as above was added to a stirred mixture of the tetrazine (1b) (0.468 g) in dry THF (20 ml) at −70 °C. The red colour of the tetrazine disappeared at once and the resultant brown solution was stirred while the temperature was allowed to rise to room temperature (*ca.* 2 h). The solution was then poured into dilute hydrochloric acid (1M; 200 ml) and extracted with ethyl acetate. The aqueous phase was basified with ammonia (*d* 0.88), filtered, and extracted with chloroform. The $^{1}$H n.m.r. (90 MHz) spectrum of the dried extract ($MgSO_4$) showed the presence of both di-isopropylamine and isopropylamine (see Scheme 4), the latter being confirmed by augmentation of the n.m.r. signals by addition of authentic isopropylamine. The dried ($MgSO_4$) ethyl acetate solution was separated by dry-column chromatography (silica; elution with diethyl ether) into the starting tetrazine (1b) (0.40 g) and a mixture of the dihydrotetrazine (2b) and 4-methyl-3,6-diphenylpyridazine (11a) (0.185 g). These were then separated by preparative t.l.c. (silica; elution with diethyl ether); the dihydrotetrazine (2b) was isolated in its oxidized form as the tetrazine (1b) (0.08 g). The pyridazine (11a) had m.p. 134—136 °C (lit.,[11] 136—137 °C) (from diethyl ether) and was identical with an authentic sample prepared from the tetrazine (1b) and propenyl propyl ether by the method of Sauer.[11]

*Action of LDA on* 3,6-*Bis*-(4-*chlorophenyl*)-s-*tetrazine* (1c).—Under dry nitrogen, a solution of LDA (0.0015 mol), prepared as above, was added to a stirred mixture of the tetrazine (1c) (0.4 g) in dry THF (10 ml) at −70 °C. The red colour of the tetrazine slowly discharged as the temperature was raised to room temperature (*ca.* 2 h) and the resultant brown solution was poured into saturated aqueous ammonium chloride (200 ml). Extraction with ethyl acetate gave a suspension of a red solid in the organic layer. The solid was filtered off and shown to be the recovered tetrazine (1c) (0.14 g). The straw-coloured filtrate was kept for a few days whereupon further tetrazine (1c) (0.035 g), formed by oxidation of its dihydroderivative (2c), was deposited. The filtrate residue was separated by dry-column chromatography [diethyl ether–light petroleum (b.p. 40—60 °C), 1 : 1 v/v; silica] and yielded the *pyridazine* (11b) (0.06 g) m.p. 180—181 °C (from diethyl ether); $\delta_H$ ($CDCl_3$) 2.4 (3 H, s, $CH_3$) and 7.3—8.1 (9 H, m, aromatic protons) (Found: $M^+$, 314.036 68. $C_{17}H_{12}Cl_2N_2$ requires $M$, 314.037 74).



(13)

*Action of Lithium Diethylamide on* 3,6-*Diphenyl*-s-*tetrazine* (1b).—Under dry nitrogen a solution of lithium diethylamide (0.004 mol), prepared as above, was added to a stirred mixture of the tetrazine (1b) (0.47 g) in dry THF (15 ml) at −70 °C. The red colour of the tetrazine disappeared at once and the resultant brown solution was stirred as the temperature was allowed to rise to room temperature (*ca.* 2 h). The solution was then poured into saturated brine (200 ml) whereupon the red colour immediately returned. Extraction of this solution with ethyl acetate yielded, after the extract had been dried ($MgSO_4$) and evaporated, a mixture which was separated by dry-column chromatography [diethyl ether–light petroleum (b.p. 40—60 °C), 1 : 1 v/v; silica] to yield (among other, trace products) the recovered tetrazine (1b) (0.29 g), the dihydrotetrazine (2b) (0.084 g), and 3,6-diphenylpyridazine (13) (0.005 g). Compound (13) had m.p. 215—220 °C (lit.,[11] 220—222 °C), and was identical with an authentic sample, m.p. 218—220 °C (from toluene), prepared by the method of Sauer [11] from the tetrazine (1b) and ethyl vinyl ether.

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