The mechanisms of dilithiation reactions in organic syntheses: a case study based on the syntheses of ketene dithioacetals

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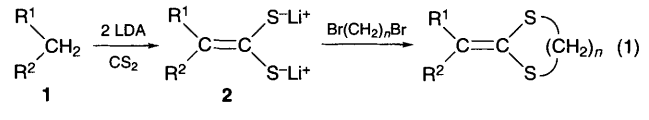
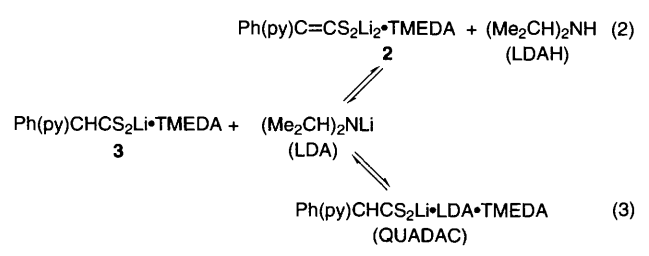
An investigation of the lithiation and CS_2-insertion reactions of $R^1R^2CH_2$ precursors (reactions used in the syntheses of ketene dithioacetals) leads to the crystal structure determination of the monolithiated complexes $R^1R^2CHCS_2Li$·TMEDA, 3 (R^1 = Ph, R^2 = pyridyl) and 4 (R^1 = H, R^2 = 2-methylpyrazine); attempted second lithiation of 3 fails to give the $R^1R^2C{=}CS_2Li_2$ species anticipated in the mechanism of reactions of this type, but synthetic and ^{1}H NMR spectroscopic evidence indicates that 4 can be lithiated further.

Many organic syntheses are proposed to involve dianions generated by the use of organolithium reagents.[1] However, doubts have arisen as to whether such dilithiations actually occur. For example, although treatment of $PhCH_2CN$ with 2 equiv. of LDA [Pr^i_2NLi] followed by D_2O incorporated 1.6–1.8 D atoms per molecule, NMR studies showed that only one CH_2 proton was being replaced by lithium in the initial treatment.[2] One explanation given was that a quasi-dianion complex (QUADAC) is formed, *i.e.* an aggregate of the monolithiated species and the second equivalent of the lithiating reagent, in this instance PhCHCNLi·LDA.[2,3] Such could react with 1 equiv. of added electrophile E^+X^-, removing one Li^+ as LiX; a rapid intra-aggregate lithiation, then reaction with the second equivalent of electrophile, would account for the final disubstituted product. More recently,[4] we also were unable to isolate or detect dilithium intermediates during the α-lithiation of lithium carbamates. However, we suggested that such intermediates might exist in low concentrations within a (monolithiate + Li reagent) ⇌ dilithiate equilibrium, a fast reaction between the dilithium species and added electrophile then driving this equilibrium forward. To explore these mechanistic possibilities further, we have investigated a protocol established for the preparation of ketene dithioacetals,[5] eqn (1). We reacted 2-benzylpyridine (**1**, R^1 = Ph, R^2 = pyridyl) and 2,3-dimethylpyrazine (**1**, R^1 = H, R^2 = 2-methylpyrazine) in THF with 1 equiv. LDA and CS_2. Treatment of the initial products with TMEDA [$Me_2N(CH_2)_2NMe_2$] gave complexes of monolithium species $R^1R^2CHCS_2Li$,† whose crystal structures (**3** and **4**, respectively) are reported.‡ Attempts were then made to prepare or to detect spectroscopically dilithium species of type **2**.





2-Benzylpyridine was added to an equimolar amount of LDA in THF at −78 °C. After warming slightly 1 equiv. CS_2 was added, giving a red solution. The solvent was removed and the residue dissolved in hot toluene containing TMEDA. Subsequent cooling afforded red crystals identified as Ph(Py)CHCS_2Li·TMEDA, **3**. The structure, Fig. 1, is the first for a lithium dithiacarboxylate, although a related lithium dithiacarbamate Ph_2NCS_2Li·2THF is known,[4] and shows CS_2 chelation of Li^+. In **3**, however, only one S atom bonds to Li^+ [Li–S(1) 2.438(4) Å] which is also bonded to the pyridyl-N as part of a six-membered LiSCCCN ring [Li–N(1) 2.057(5) Å] and to the two N centres of TMEDA. The second S atom, S(2), is uninvolved with Li^+, implying that the inserted CS_2 might be viewed as S(2)=C–S(1)$^-$. However this is not so, the C–S(1) and C–S(2) distances being 1.687(3) and 1.673(3) Å respectively, *i.e.* there is almost uniform delocalisation.

Complex **4**, (2-$MeC_4H_2N_2$)CH_2CS_2Li·TMEDA, was obtained in a similar manner to **3**.† In the solid‡ the basic unit is a monomer [Fig. 2]. Monolithiation and CS_2 insertion have again occurred although, in contrast to **3**, both S centres bond to Li^+ [Li–S(1) 2.554(4), Li–S(2) 2.688(5) Å]. The C–S distances are similar [C(1)–S(1) 1.687(3), C(1)–S(2) 1.675(3) Å] and essentially identical to those in **3** despite the fact that there only one S centre bonds to Li^+. These monomers of **4** then polymerise by means of interactions between each Li^+ and a pyrazine N (the N *ortho* to the intact Me group) in a neighbouring monomer [Li···N 2.129(5) Å].

We then attempted to obtain or detect dilithiated species **2** [see eqn. (1)]: (i) preparatively, by taking **1** with 2 equiv. of LDA, one of CS_2 and excess TMEDA, or by reacting pre-isolated **3** and **4** with further LDA and TMEDA; (ii)

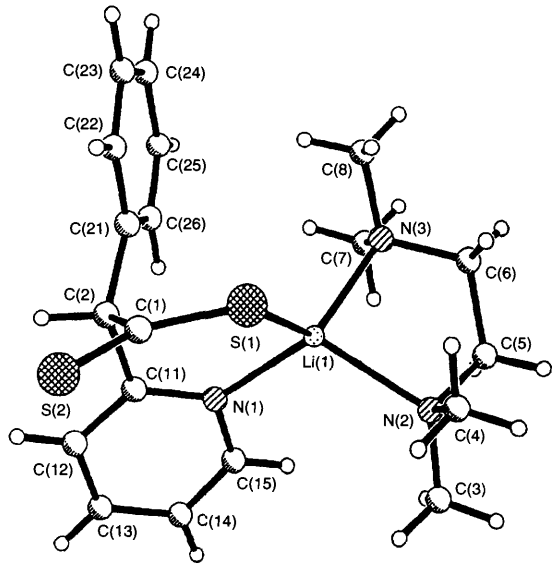


Fig. 1 Molecular structure of **3**

spectroscopically, by treating solutions of **3** and **4** with 1 equiv. LDA, and then recording resulting ^{1}H NMR spectra at 25 °C. For 2-benzylpyridine the results seem clear-cut. Its reaction with 2 equiv. LDA, CS_2 and TMEDA results only in the high yield isolation of the monolithium complex **3**. Treatment of **3** itself in THF with further LDA and TMEDA led simply to its near-quantitative recovery. In neither instance could we isolate a genuine dilithium species **2**, eqn. (2), or a QUADAC, eqn. (3).

Such findings do not of course preclude the existence of one or both of these species in solution: they might not crystallise from solution, or they might simply be present in very low equilibrium concentrations. To help probe these possibilities we recorded the ^{1}H NMR spectrum of a 1 : 1 mixture of **3** and LDA in $[^2H_6]Me_2SO$. This spectrum is merely a superposition of the individual spectra of the two components. Most significantly, the C(2)–H proton (see Fig. 1) is at the same position (δ 6.16) as in **3** (δ 6.17) and it integrated (within the usual limits of accuracy) as 1 H exactly. The evidence from these experiments suggests that dilithium species are not formed or that their equilibrium concentrations are very low.

Results for 2,3-dimethylpyrazine point to very different behaviour. Its treatment in THF with 2 equiv. of LDA, CS_2 and TMEDA gave a solution from which we could isolate only the monolithium complex **4**. However, reacting pre-isolated **4** in THF with a further equiv. each of LDA and TMEDA afforded an orange precipitate. Preliminary results indicate that it is impure (2-methylpyrazinyl)CH=CS_2Li_2·3THF. Pertinent features are (i) the precipitate does not contain LDA, *i.e.* it is not a QUADAC, and (ii) the CH_2 group of **4** has become an alkenyl CH group. For cleaner findings we resorted again to a ^{1}H NMR experiment, taking a 1 : 1 mixture of **4** and LDA in $[^2H_6]Me_2SO$. The ^{1}H NMR spectrum of **4** alone [Fig. 3(*a*)] contains two

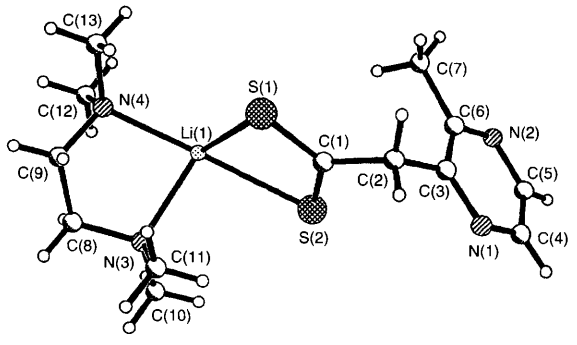


Fig. 2 Molecular structure of **4**

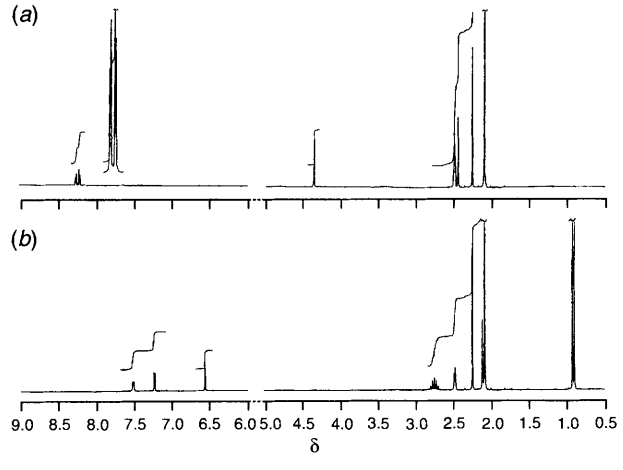


Fig. 3 (*a*) ^{1}H NMR spectrum of **4**. (*b*) ^{1}H NMR spectrum of **4** after reaction with LDA.

irregular multiplets due to the two pyrazine ring protons, a singlet due to the intact Me group (δ 2.46) and another singlet for the lithiated CH_2 group (δ 4.38). After treatment with LDA the spectrum changes [Fig. 3(*b*)] markedly and quantitatively. The pyrazine ring proton resonances are now more widely spaced and regular doublets. The Me group is still intact (δ 2.14). Crucially, though, the CH_2 group resonance (δ 4.38) has gone, and has been replaced by a –CH= resonance (δ 6.56, integral 1 H). Remaining resonances are due to TMEDA (two singlets at δ 2.27, 2.11) and LDAH (a septet centred at δ 2.73 and a doublet δ 0.92; the NH resonance is below the residual proton of the $[^2H_6]Me_2SO$. The combination of preparative and spectroscopic results implies that a genuine (non-QUADAC) dilithiation has taken place in this particular system.

We thank the EPSRC and the Associated Octel Co. Ltd. (S. C. B., I. C.-H.), St. John's College, Cambridge (Research Fellowship, M. G. D.), and The Royal Society (P. R. R.) for financial support.

Footnotes

† *Experimental data* for **3**: 2-benzylpyridine (**1**, R^1 = Ph, R^2 = pyridyl; 0.43 g, 2.5 mmol) was added to a solution of LDA (0.27 g, 2.5 mmol) in THF (6 ml) at −78 °C. The resulting dark red solution was warmed slightly prior to addition of CS_2 (0.15 ml, 2.5 mmol). Solvent was then removed from the orange solution and the residue was dissolved in warm toluene (10 ml) containing TMEDA (0.75 ml, 5 mmol). Cooling the red–orange solution afforded red crystals of **3**, Ph(Py)$CHCS_2Li$·TMEDA. First batch yield, 0.76 g (83%), mp 138–140 °C.

For **4**: The complex was obtained on a 2.5 mmol scale in a manner analogous to **3**, reacting 2,3-dimethylpyrazine (**1**, R^1 = H, R^2 = 2-methylpyrazine; 0.27 g) with LDA in THF and then with CS_2. Solvent removal and recrystallisation from toluene containing TMEDA gave red crystals of **4**, (2-$MeC_4H_2N_2$)CH_2CS_2Li·TMEDA. First batch yield, 0.29 g (38%), mp 152–155 °C.

‡ *Crystal data* for **3**: Ph(Py)$CHCS_2Li$·TMEDA, $C_{19}H_{26}LiN_3S_2$, M = 367.49, monoclinic, space group Cc, a = 13.863(3), b = 9.906(2), c = 14.347(3) Å, β = 90.77(3)°, V = 1970.1(7) Å^3, $F(000)$ = 784, λ(Mo-Kα) = 0.71073 Å, μ(Mo-Kα) = 0.276 mm^{-1}, T = 153(2) K, Z = 4, D_c = 1.239 Mg m^{-3}. Data were collected on a Stoe-Siemens diffractometer in the range 3.79 ≤ θ ≤ 22.49° (1980 reflections collected, 1407 independent reflections). R_1 = 0.0199 for 1356 reflections with [$F > 4\sigma(F)$] and wR_2 = 0.0519 for all data. Absolute structure parameter = 0.01(7).

For **4**: (2-$MeC_4H_2N_2$)CH_2CS_2Li·TMEDA, M = 306.41, orthorhombic, space group $Pccn$, a = 22.613(3), b = 10.602(1), c = 14.152(2) Å, V = 3392.8(7) Å^3, $F(000)$ = 1312, λ(Mo-Kα) = 0.71073 Å, μ(Mo-Kα) = 0.309 mm^{-1}, T = 153(2) K, Z = 8, D_c = 1.200 Mg m^{-3}. Data collection (range 3.58 ≤ θ ≤ 25.00°; 3373 reflections collected, 2987 independent reflections) and structure solution and refinement as for **3**, to R_1 = 0.0444 for 2251 reflections with [$F > 4\sigma(F)$] and wR_2 = 0.1031 for all data. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/108.

References

1 B. J. Wakefield, *Organolithium Methods*, Academic Press, London, 1988; L. Brandsma, *Preparative Polar Organometallic Chemistry*, Springer-Verlag, Berlin, 1990, vol. 2; C. M. Thompson, *Dianion Chemistry in Organic Synthesis*, CRC Press, Boca Raton, Florida, 1994.

2 P. J. Crowley, M. R. Leach, O. Meth-Cohn and B. J. Wakefield, *Tetrahedron Lett.*, 1986, **27**, 2909; P. R. Carlier, B. L. Lucht and D. B. Collum, *J. Am. Chem. Soc.*, 1994, **116**, 11 602.

3 W. Zarges, M. Marsch, K. Harms and G. Boche *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1392; G. Boche, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 277.

4 S. C. Ball, I. Cragg-Hine, M. G. Davidson, R. P. Davies, A. J. Edwards, I. Lopez-Solera, P. R. Raithby and R. Snaith, *Angew Chem., Int. Ed. Engl.*, 1995, **34**, 921.

5 J. A. Goodwin, I. Kwok and B. J. Wakefield, *Synthesis*, 1990, 991.

Received, 8th March 1996; Com. 6/01664B