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A new mode of cyclobutenedione ring opening for the synthesis of 2-oxobut-3-enamides and tetrasubstituted furans†

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A dichotomy between the additions of organolithiums and lithium amides to cyclobutenediones is described wherein the former give carbonyl addition products while the latter induce ring opening by enone cleavage *via* *O*- to *C*-lithium transfer. This distinct mode of ring scission gives access to 2-oxobut-3-enamides and tetrasubstituted furans.

Cyclobutenediones and squarates, *e.g.* **1a**, are used extensively as precursors to carbocyclic and heterocyclic ring systems through ring expansion (Scheme 1).[1–10] Typically, a carbon nucleophile is first added to give an adduct **2** that rearranges to a product on thermolysis or photolysis. Rearrangements triggered by light usually give rise to 5*H*-furanones **6** *via* vinylketene (*E*)-**4**,[9,10] while those triggered by heat typically proceed *via* the isomeric vinylketene (*Z*)-**4** and give products determined by the nature of the residue introduced at C4. The versatility and reliability of the chemistry is evident from the frequent deployment of such rearrangements in natural products total synthesis.[5,8]

Herein we describe a dichotomy between the additions of organo-lithiums and lithium amides to cyclobutenediones (Scheme 1). Thus, while dimethyl squarate **1a** gives cyclobutenones **2** on treatment with organolithum reagents its reactions with lithium amides lead to vinyllithium intermediates **5** *via* the corresponding adduct **3**. Herein we show how this unprecedented mode of ring opening, involving scission of the C3–C4 bond with concomitant *O*- to *C*-lithium transfer, provides access to an array of 2-oxo-but-3-enamides 7 and tetrasubstituted furans **8**.

The discovery was made while preparing a series of 3-amino-4-methoxycyclobutenediones by the addition of amines to dimethyl squarate **1a** (Scheme 2).[9] Though the method worked well for many substrates, *e.g.* **1a** to **9a–c**, it returned starting materials when applied to 2°-amines with a high steric burden, *e.g.* $^{i}Pr_2NH$.[11] This prompted a switch to using LDA as the nucleophile, but instead of delivering the anticipated 3-aminocyclobutenedione **9d**, 2-oxo-but-3-enamide **7a** was isolated as the major product in 65% yield. Intrigued by this finding, we decided to explore the generality of the reaction, beginning with extensions to diisopropyl and di-*tert*-butyl squarates, **1b** and **1c**. Pleasingly, both gave the corresponding 2-oxo-but-3-enamides, **7b** and **7c**, albeit more slowly due to the increase in steric demand.

The reaction was next extended to 2-alkoxy-3-amino-cyclobuten-ones **9**. All of the cases examined (Table 1) showed excellent regioselectivity leading to the corresponding vinylogous amides **11** exclusively. This outcome can be attributed to a preferred addition of LDA to the vinylogous ester carbonyl in **9**, leading to adduct **10**, over its addition to the vinylogous amide carbonyl.

Steric influences on the reaction were next examined with respect to the lithium amide (Scheme 3). Notably, while LDA and lithium piperidide each induced ring opening of cyclobutenedione **9a** to 2-oxo-but-3-enamides **11a** and **12a** respectively, starting material was returned when bulkier lithium amides were employed, *e.g.* LiHMDS, lithium 2-methylpiperidide and LiTMP. By way of contrast, lowering steric demand with lithium dimethylamide promoted substitution of the alkoxide leading to the bis-aminocyclobutenedione **13b**.

Lithium amide additions to dimethyl squarate **1a** could also be sequenced with substitution of the terminal alkoxide for NH_2 through employment of an ammoniacal work up (Scheme 4).[12]

Reactions of 3-alkoxy-4-alkylcyclobutenediones **16** with LDA and lithium piperidide were next examined and exposed further subtleties (Scheme 5). Thus, while treatment of the *tert*-butyl derivative **16a** with LDA gave the anticipated oxobutenamide **18a**, substitution dominated with lithium piperidide leading to amino-cyclobutenedione **17**. Reducing steric demand with the methyl analogue **16b** led to cleaner reactions and higher yields, with lithium piperidide giving oxobutenamide **18b** in 79% yield.

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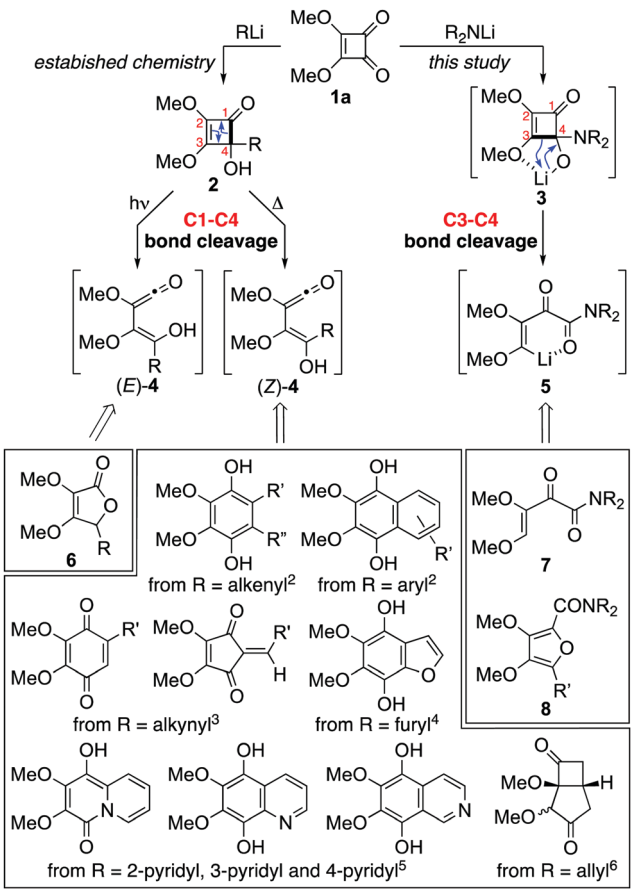
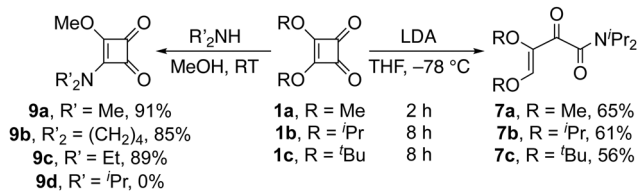


Scheme 1 The dichotomous reactivity of dimethyl squarate with organolithiums and lithium amides, and a summary of key transformations.



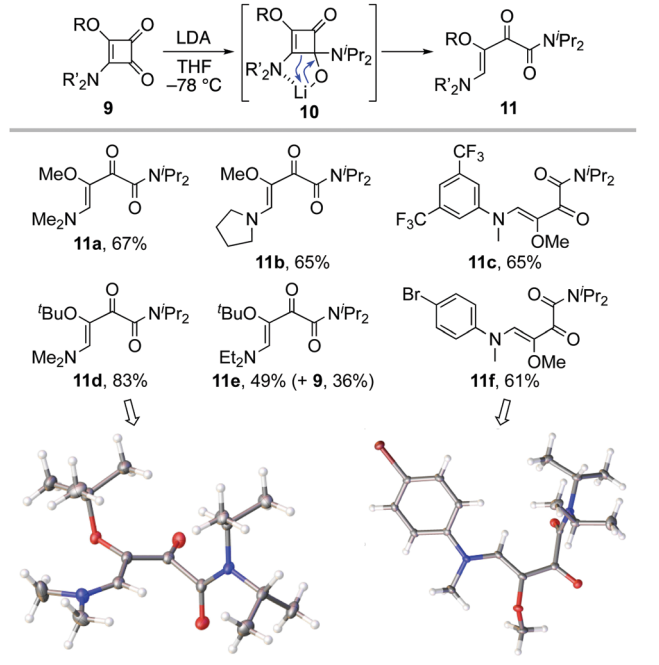
Scheme 2 The discovery of the C3–C4 mode of ring scission.

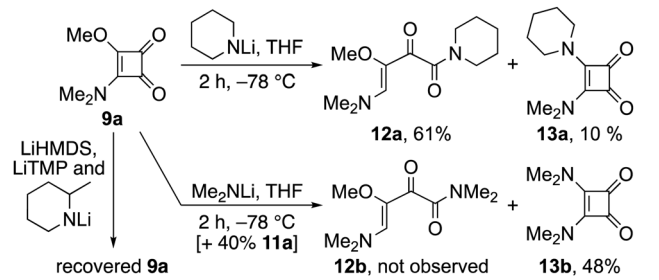
Curiously, alkene reduction to the sensitive cyclobutanedione **19** was observed following exposure to LDA.[13]

A DFT analysis on the opening of adducts **3a** (Fig. 1) and **21** (Fig. 2), to vinyllithium intermediates **5a** and **23** respectively, identified low energy pathways for ring scission *via* transition states **20** and **22**.[14] From these calculations we infer that the facile *O*- to *C*-lithium transfer is due to both a relief of ring strain and the formation of an amide that co-ordinates strongly to the resulting vinyllithium.

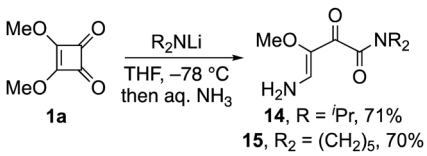
The intermediacy of vinyllithium species led us to seek an extension of the chemistry for the synthesis of tetrasubstituted furans. To that end, dimethyl squarate **1a**, diisopropyl squarate **1b** and cyclobutene-dione **9a** were each treated sequentially with LDA then an aldehyde. We presume each reaction

Table 1 Reactions of LDA with aminocyclobutenones together with X-ray structures for **11d** [CCDC 2059384] and **11f** [CCDC 2042398]





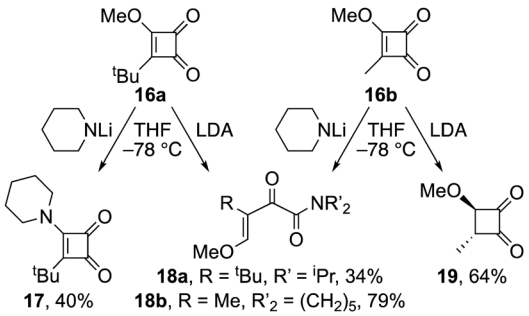
Scheme 3 Influence of steric factors on the addition of lithium amides to cyclobutenedione **9a**.



Scheme 4 Substitution of the terminal ether for NH_2 with an ammoniacal work-up.

proceeded *via* adduct **24**, as the corresponding furans **8** were given in modest yields following an aqueous work-up and purification by column chromatography (Table 2). Notably, these furans each bear three electron-donating substituents making them difficult to access by traditional methods.[15]

Finally, we have identified a single example of the C3–C4 mode of ring scission occurring during an amine addition to a cyclobutenedione.[9] It was observed when 3-isoproxycyclobutenedione **25**



Scheme 5 Reactions of 3-alkoxy-4-alkylcyclobutenediones with lithium piperidide and LDA.

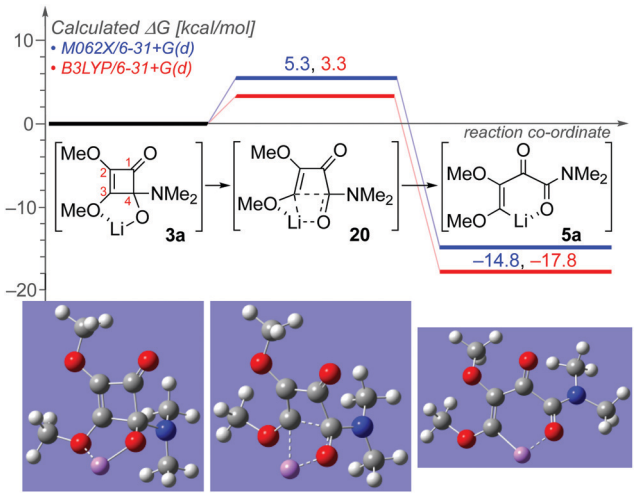


Fig. 1 Summary of DFT calculations on the opening of dimethyl squarate **1a** with lithium dimethylamide.

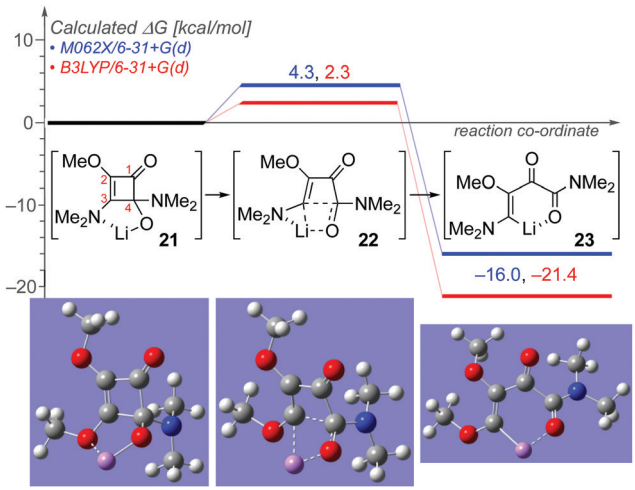


Fig. 2 Summary of DFT calculations on the opening of cyclobutenedione **9a** with lithium dimethylamide.

was treated with benzylamine, where 2-oxo-but-3-enamide **27** (Fig. 3) was as a significant byproduct formed in 25% yield alongside with the anticipated aminocyclobutenedione **26**

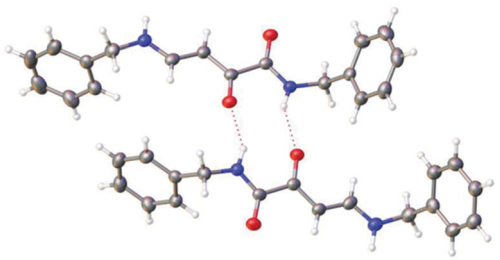
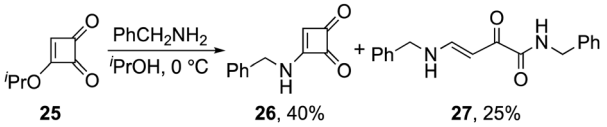
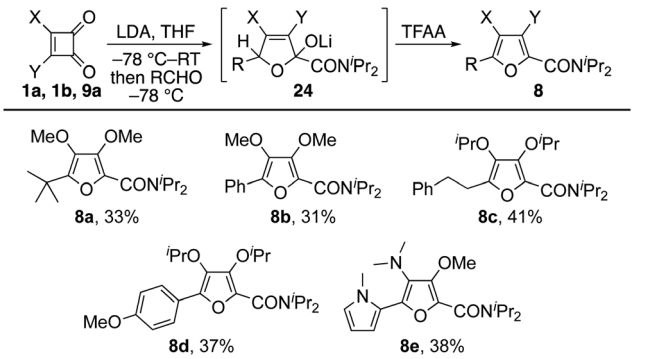


Fig. 3 X-ray crystal structure of 2-oxo-but-3-enamide **27** [CCDC† 1500038].



Scheme 6 A related fragmentation of cyclobutenedione **25** triggered with benzylamine.

Table 2 Three-component coupling reactions leading to tetrasubstituted furans



(40% yield). To the best of our knowledge, this side reaction has not been reported previously (Scheme 6).

In conclusion, we have uncovered a new mode of cyclobutenedione ring opening that is triggered by lithium amide addition. The reaction proceeds *via* sequential *N*- to *O*- to *C*-lithium transfer, as detailed in Scheme 1, and gives access to an array of 2-oxo-but-3-enamides (*via* protonation) and tetrasubstituted furans (*via* aldehyde addition). We are currently investigating further extensions of the methodology in heterocyclic synthesis.

Dr Wei Sun and Ryan Bennett contributed equally in respect of the experimental work with Dr Mark Light performing the X-ray analyses and Prof. David Harrowven supervising the work.

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Conflicts of interest

There are no conflicts of interest to declare.

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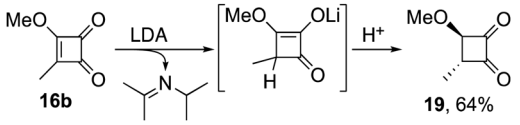

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