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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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COMMUNICATION

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-oxo-but-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). 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 SH-furanones 6 via vinylketene (E)-4, 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.

Herein we describe a dichotomy between the additions of organolithiums and lithium amides to cyclobutenediones (Scheme 1). Thus, while dimethyl squarate 1a gives cyclobutenones 2 on treatment with organolithium 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-methoxycyclobutenones by the addition of amines to dimethyl squarate 1a (Scheme 2). 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. iPr2NH. This prompted a switch to using LDA as the nucleophile, but instead of delivering the anticipated 3-aminocyclobutenone 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-cyclobutenones 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.

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ARTICLE

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

Table 1 Reactions of LDA with aminocyclobutenones together with X-ray structures for 11d [CCDC2059384] and 11f [CCDC2042398].

| Reagent | Product | Yield % |
|---------|---------|---------|
| Me₂N    | 11a     | 67%     |
| Me₂N    | 11b     | 65%     |
| Bu₂N    | 11c     | 65%     |
| Me₂N    | 11d     | 83%     |
| Bu₂N    | 11e     | 49% (+ 9, 36%) |
| LiHMDS  | 11f     | 61%     |

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 NH₂ 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. Curiously, alkene reduction to the sensitive cyclobutanedione 19 was observed following exposure to LDA.11

A DFT analysis on the opening of adducts 3a (Figure 1) and 21 (Figure 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 best of our knowledge, this side reaction has not been
with the anticipated aminocyclobutenedione
of ring scission occurring during an amine addition to a cyclobut-
was as a significant byproduct formed in 25% yield alongside
25
was treated with benzylamine, where 2-oxo-but-3-enamide
dione.
Finally, we have identified a single example of the C3-C4 mode
of ring scission occurring during an amine addition to a cyclobut-
edione. It was observed when 3-isoproxycyclobutenedione
25 was treated with benzylamine, where 2-oxo-but-3-enamide
8a, 33%
8b, 31%
8c, 41%
8d, 37%
8e, 38%
27
Finally, we have identified a single example of the C3-C4 mode
of ring scission occurring during an amine addition to a cyclobut-
edione. It was observed when 3-isoproxycyclobutenedione
25 was treated with benzylamine, where 2-oxo-but-3-enamide
27 was as a significant byproduct formed in 25% yield alongside
with the anticipated aminocyclobutenedione 26 (40% yield). To
the best of our knowledge, this side reaction has not been
reported previously (Scheme 6).

Table 2 Three-component coupling reactions leading to tetrasubstituted furans

| Reaction | Product |
|----------|---------|
| 1a, 1b, 9a | 8a, 33% |
| -78 °C | TFCA |
| -78 °C | LDA, THF |
| 8b, 31% | PhO|
| 8c, 41% | PhO|
| 8d, 37% | PhO|
| 8e, 38% | PhO|

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

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 proceeded via adduct 24, as the
Table 2 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

In conclusion, we have uncovered a new mode of cyclobutene-
dione 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.

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