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Reaction of Cyclic α-Oxoketene Dithioacetals with Methylene Isocyanides: A Novel Pyrrole Annulation–Ring-Expansion Domino Process

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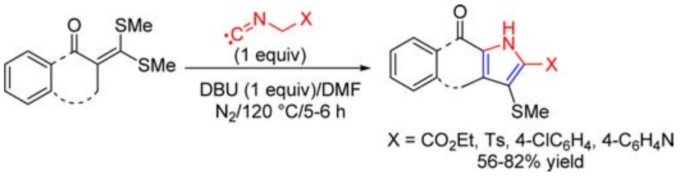
ABSTRACT



The title reaction provides a direct entry to a range of biologically relevant annulated pyrroles via a domino process involving a regioselective one-carbon homologation of cyclic ketones as the key step.

Oligosubstituted pyrroles represent an important class of five-membered heterocycles, being basic constituents of numerous natural products,[1] potent pharmaceuticals,[1,2] molecular sensors, and devices.[2,3] Similarly, condensed pyrroles such as indolequinones and pyrroloquinolones have attracted considerable attention owing to the significant biological activity associated with compounds containing these heterocyclic cores. Thus, naturally occurring mitomycin C (MMC) bearing an indolequinone pharmacophore has been in clinical use since 1970 for treatment of various types of tumors,[4] whereas other MMC analogues (apaziquone,[5] ES 936, BE-10988) are used in the advanced stage of treatment for various kinds of cancers.[4−6] Similarly, increasing interest has been devoted in recent years to pyrrolo[3,2-*c*]quinolin-4-ones,[7] since several of its analogues are found in biologically important natural products such as martinelline and martinellic acid,[8−10] displaying a broad spectrum of biological

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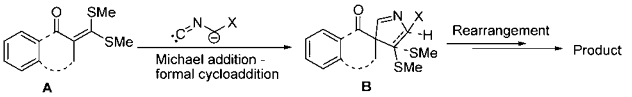
activity.[9b,11−14] On the other hand, the pyrrolo[2,3-*c*]quinolone framework has not been much explored,[15] whereas the corresponding previously unknown linear pyrrolo[3,2-*b*]quinolone ring system has been only recently synthesized.[16]

One of the useful and versatile methods for the synthesis of oligosubstituted pyrroles involves base mediated formal cycloaddition of activated methylene isocyanides with various Michael acceptors.[17] Since the initial discovery by Schollkopf and Gerhart about 45 years ago,[18a] α-metalated isocyanides have emerged as useful synthons, participating in various type of cocyclizations with a range of multiple bonds and other reactive species, leading to a diverse array of nitrogen heterocycles.[18b,c,19] Also, great progress has been made in the use of transition metal, especially copper catalyzed reactions of various methylene isocyanides with activated double and triple bonds.[9b,20−22] Recently, substituted pyrroles have also been obtained by silver catalyzed cycloaddition of isocyanoacetates with unactivated terminal alkynes.[2d,23] As part of our program, to develop new synthetic methods[24] for construction of small molecule heterocycles with potential biological activity, we have previously reported efficient synthesis of 2,3,4-substituted pyrroles[17] and imidazo[1,5-*a*]quinoxalines[24i] by formal cycloaddition of activated methylene isocyanide anions to polarized ketene dithioacetals and 2,3-substituted quinoxalines, respectively.[25] Recently, we have also described a novel Cu(I) catalyzed domino reaction of 2-aryl-4-[(methylthio)(het/aryl)-methylene]-5-oxazolones with various methylene isocyanides providing a direct straightforward route to hitherto unreported 2,5,4′-trisubstituted-4,5′-bisoxazoles.[24c] In an effort to extend this type of chemistry, we were prompted to examine the reaction of cyclic oxoketene dithioacetals **A** with various activated methylene isocyanides. At the outset, it was anticipated that the reaction of **A** with methylene isocyanide anions might yield first the strained spiroheterocycles such as **B**, which might undergo further reaction/rearrangement including cleavage of cyclic ketones (Scheme 1). Indeed, when few of the selected cyclic α-oxoketene dithioacetals reacted with various activated methylene isocyanides in the presence of DBU as base, the isolated products were found to be annulated pyrroles with diverse structural features, formed through a mechanistically interesting, multistep domino process involving one carbon ring expansion of cyclic ketones as the key step. The results of these studies are reported in this communication.

Scheme 1. Proposed Reaction of Cyclic Oxoketene Dithioacetals and Methylene Isocyanide



The reaction of cyclic oxoketene dithioacetal **1** derived from 1,3-indanedione with ethyl isocyanoacetate (**2a**) was first examined in the presence of various bases (DBU, *t*-BuOK, NaH, Cs_2CO_3) and solvents for optimization of reaction conditions leading to the formation of observed product/s (Table S1, Supporting Information). Thus, under optimized conditions when **1** (1 equiv) was reacted with **2a** (1 equiv) in the presence of DBU (1 equiv) as a base in DMF at 120 °C, workup of the reaction mixture furnished only one product (80%), which was characterized as 2-[carbethoxy-3-(methylthio)]pyrrolo[2,3-*b*]napthoquinone **3** (Scheme 2). Under identical conditions, the reaction of **1** with tosylmethyl isocyanide (**2b**) also furnished the corresponding tosyl-substituted pyrrolonapthoquinone **4** in 76% yield (Scheme 2). The structure of **4** was further confirmed with the help of X-ray crystallographic data. Similarly, further diversity at 2- position of the pyrrolonapthoquinone

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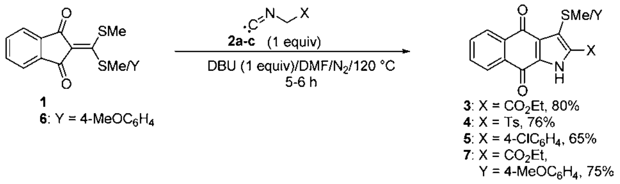
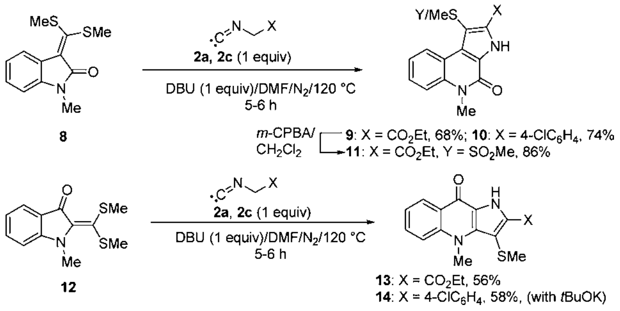
was introduced by reacting **1** with 4-chlorobenzyl isocyanide **2c** under similar conditions, affording 2-(4-chlorophenyl)-substitiuted pyrrolonapthoquinone **5** in 65% yield. Interestingly, the 2-[(methylthio)(4-methoxyphenyl)methylene]-1,3-indanedione **6** also reacted smoothly with ethyl isocyanoacetate under identical conditions, yielding substituted pyrrolonapthoquinone **7** in 75% yield (Scheme 2).

Scheme 2. Reaction of **1** and **6** with Methylene Isocyanides **2a**−**c**



The generality and scope of this unusual rearrangement was examined by reacting a few selected cyclic ketene dithioacetals with various activated methylene isocyanides as shown in Schemes 3−6. Thus, when the cyclic *S*,*S*-acetal **8** from 2-oxindole was subjected to reaction with methylene isocyanides **2a** and **2c** under optimized conditions, product analysis revealed that the reaction follows a similar pattern as **1**, furnishing the corresponding substituted pyrrolo[2,3-*c*]quinolones **9** and **10** in good yields (Scheme 3). The structure of **9** was further confirmed by X-ray crystallographic data of the product **11** obtained by *m*-CPBA oxidation of **9**.

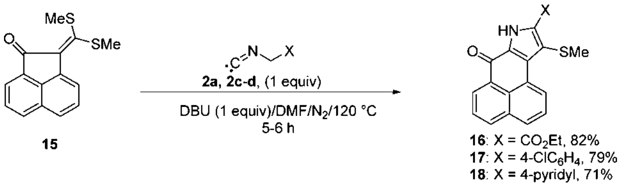
Scheme 3. Synthesis of Substituted Pyrrolo[2,3-*c*]quinolones and Pyrrolo[3,2-*b*]quinolones



The reaction of ketene dithioacetal **12** from 3-oxindole with **2a** and **2c** similarly provided linearly substituted pyrrolo[3,2-*b*]quinolones **13**−**14** although in moderate yields because of the poor solubility of products in most of solvents (Scheme 3).

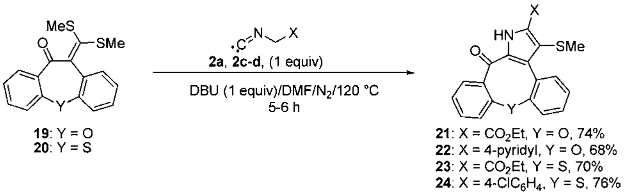
The reaction was next extended to oxoketene dithioaceteal **15** derived from acenaphthenone, which also followed a similar course, involving pyrrole annulation, along with ring expansion of the five-membered cyclic ketone, thus providing novel tetracyclic indole derivatives **16**−**18** in high yields, on treatment with various methylene isocyanides **2a**, **2c** and 4-pyridylmethyl isocyanide **2d**, respectively, under identical conditions (Scheme 4).

Scheme 4. Synthesis of Tetracyclic Indoles **16**−**18**



To further evaluate the generality and scope of this unexpected rearrangement for the construction of novel large ring pyrrole annulated heterocycles, the reaction of α-oxoketene dithioacetals **19**−**20** (from dibenzoxepin-10-one and dibenzothiepin-10-one, respectively), with various methylene isocyanides **2a**,**c**,**d** was examined (Scheme 5). Indeed, to our delight, the reaction proceeded as expected, with the formation of tetracyclic pyrrolo-fused dibenzooxocinone and dibenzothiocinone derivatives **21**−**24** in high yields (Scheme 5).

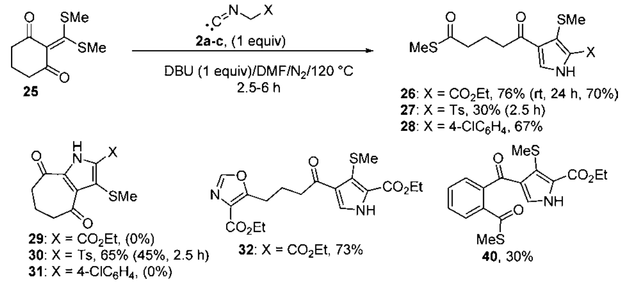
Scheme 5. Synthesis of Pyrrole-Annulated Dibenzoxacinone and Dibenzothiocinone



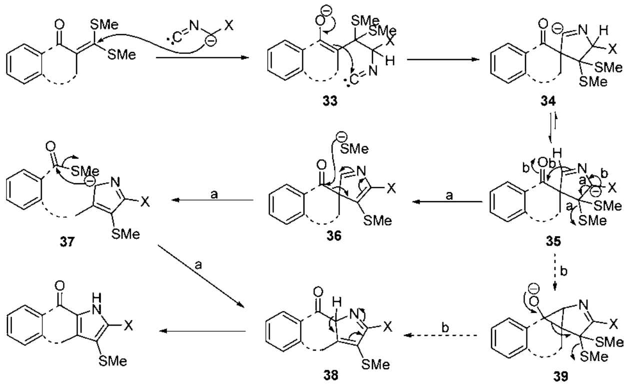
Interestingly, the ketene dithioacetal **25** from 1,3-cyclohexanedione behaved differently, when reacted with 1 equiv of ethyl isocyanoacetate (**2a**) under identical conditions, and no trace of ring-expanded pyrrolo-fused 1,3-cycloheptanedione **29** was detected in the reaction mixture. The product isolated was characterized as 2-carbethoxy-3-(methylthio)pyrrole-4-[(5-oxo)pentane]carbothioate **26** (76%) (Scheme 6). On the other hand, treatment of **25** with tosylmethyl isocyanide **2b** (1 equiv) under identical conditions (DBU/DMF,120 °C, 6 h) furnished the pyrroloannulated cycloheptanedione **30** in 65% yield, whereas disrupting the reaction after 2.5 h afforded the corresponding pyrrolocarbothioate **27** (30%) along with **30** (45%) (Scheme 6). The reaction of **25** with 4-chlorobenzyl isocyanide **2c** also yielded the corresponding 2-(4-chlorophenyl)pyrrole carbothioate **28** (67%) under identical conditions, with no trace of the corresponding pyrroloannulated product **31**. Interestingly, when **25** was reacted with two equiv of ethyl isocyanoacetate **2a** in the presence of DBU (2 equiv) in DMF at 120 °C for 5 h, the isolated product was characterized as the four carbon tethered pyrrole/oxazole derivative **32** (73%) which is evidently formed by addition-cyclization of **2a** to carbothioate functionality in **26** (Scheme 6).

The probable mechanism for the formation of various annulated pyrroles from the corresponding cyclic oxoketene

Scheme 6. Reaction of **25** with Methylene Isocyanides



Scheme 7. Proposed Mechanism for the Formation of Annulated Pyrroles



dithioacetals is shown in the Scheme 7. Thus initial 1,4-conjugate addition of methylene isocyanide carbanion to oxoketene dithioacetal followed by intramolecular cyclization of the adduct **33**, initially furnishes the unstable spiropyrrolenine anion **34**, which equilibriates to more stable aza-allyl anion **35**. Subsequent elimination of methylthiolate anion in **35** affords the sterically constrained spiroketone intermediate **36** (route a), which appears to undergo facile ring cleavage by nucleophilic attack of methylthiolate anion on carbonyl group of **36** yielding *ortho*-substituted carbothioate intermediate **37** with a pendant pyrrolyl carbanion. Finally, intramolecular cyclization of the intermediate **37** *via* nucleophilic attack of pyrrolyl anion (at unsubstituted carbon) on carbothioate and elimination of methylthiolate anion affords the rearranged pyrrole annulated products in good yields (route a, Scheme 7).

The above mechanism was indeed confirmed by isolation of *o*-substituted benzocarbothioate intermediate **40** in 30% yield (along with pyrrolonaphthoquinone **3**, 50%) when ketene dithioacetal **1** was reacted with isocyanoacetate **2a** (1 equiv) in the presence of DBU (1 equiv) in DMF at room temperature for 24 h (Scheme 6). The intermediate carbothioate **40** was transformed completely into pyrrolonaphthoquinone **3** (77%), when the above reaction mixture was heated at 120 °C for 5 h (Scheme 6). Further, the formation of pyrrole-4-[(5-oxo)pentane]carbothioate **26** in the reaction of ketene dithioacetal **25** (derived from 1,3-cyclohexanedione) with **2a** under identical conditions supports the suggested mechanism.[15c]

In an alternate mechanism (route b), the spiroaza-allyl anion intermediate **35** can undergo intramolecular nucleophilic attack on the carbonyl group with the formation of strained tricyclic alkoxide intermediate **39** which, on ring expansion along with elimination of methylthioate anion and isomerization of the resulting intermediate **38**, affords the observed pyrroloannulated products (route b) (Scheme 7).

In summary, we have disclosed a novel domino process involving a base-induced reaction of cyclic α-oxoketene dithioacetals with activated methylene isocyanides leading to the formation of a diverse range of annulated pyrroles along with a highly regioselective one-carbon ring expansion of cyclic ketones as the key step. The method provides facile access to biologically important fused pyrroles with structures ranging from pyrrolonapthoquinones, angular and linear pyrroloquinolones, tetracyclic fused indoles and pyrrole annulated dibenzooxocinone and dibenzothiocinone derivatives. The new strategy further opens the possibility of rational design of direct synthesis of novel annulated pyrroles through the proper choice of substrates. Also, isolation of open-chain pyrrole carbothioates such as **26**–**28** and four-carbon-tethered pyrroles/oxazoles **32** in the reaction of 1,3-cyclohexanone dithioacetal **25** with various methylene isocyanides under identical conditions (Scheme 6) makes this rearrangement more deserving and interesting for further detailed synthetic and mechanistic studies, which are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization of all compounds, and crystallographic information of compounds **4**, **11**, **16**, **17**, **21**, and **24** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.