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# An intramolecular cycloaddition approach to pyrrolo[3,2-*c*]quinolones

Yong He, Hossen Mahmud, Brian R. Wayland, H. V. Rasika Dias† and Carl J. Lovely*

*Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, TX 76019, USA*

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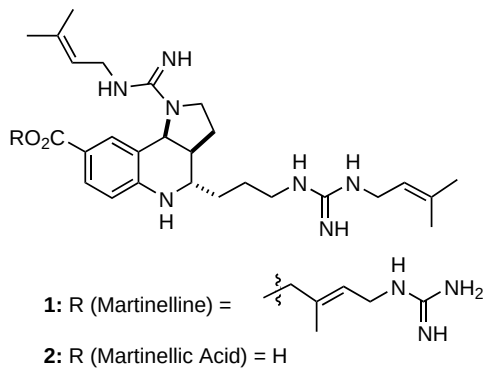
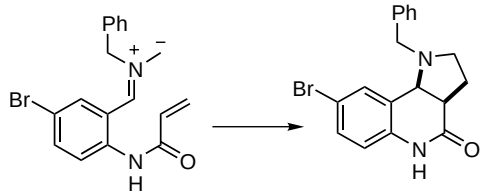
**Abstract**—An approach to pyrrolo[3,2-*c*]quinolones is described which relies on an intramolecular azomethine ylide alkene cycloaddition reaction. Critical to the success of this reaction was the requirement for alkylation of the aniline nitrogen, in the absence of this substituent a decarboxylative-Michael addition pathway was observed. 

As part of our program focused on the synthesis of bioactive polyguanidine natural products, we have been engaged in developing approaches to the total synthesis of the *Martinella* alkaloids **1** and **2**.[1] These relatively simple natural products have attracted considerable attention leading to the development of a number of approaches to the heterocyclic core[2] and most recently to two total syntheses.[3] In our approach to these targets, we identified pyrroloquinolones, such as **4**, as ideal precursors en route to the natural products and diverse analogs. It was envisioned that compounds of this type might be accessed through a [3+2] azomethine ylide–alkene cycloaddition (**3**→**4**). In this letter we report on the investigation of this approach, the observation of an unexpected sequence of events, and the development of a solution to provide the required heterocycle.




**3** **4**

The requisite cyclization precursor **7** was prepared from methyl 5-bromo-2-aminobenzoate (**5**) via reduction and chemoselective acylation of the 2-amino group. The sparingly soluble amide was converted into the benzaldehyde derivative by oxidation with $MnO_2$, providing **7** in a moderate 43% yield. When **7** was reacted with *N*-benzylglycine·HCl in DMF at reflux in the presence of $Et_3N$, the expected condensation–elimination–cycloaddition sequence did not occur. However, a new compound was formed in 40% isolated yield. Analysis of the $^1H$ NMR spectrum of the purified product indicated that the isolated material contained an *N*-methyl group, an aromatic aldehyde and a -$CH_2CH_2$- group. Based on these data, we concluded that the structure of the isolated product was in fact **8a**, resulting from the net decarboxylation and conjugate addition of *N*-methylbenzylamine to the acrylamide moiety.[4] When the reaction was repeated in boiling benzene, the same product was isolated in 68% yield. Somewhat intrigued by this result, compound **7** was reacted with *N*-methyl and *N*-(*p*-methoxybenzyl)glycine, the latter as its HCl salt. In each case analogous conjugate addition products **8b–c** were obtained in 30 and 50% yield, respectively. These exper-

* Corresponding author. Tel.: 817-272-5446; fax: 817-272-3808; e-mail: lovely@uta.edu

† Address correspondence to this author regarding the X-ray structures; e-mail: dias@uta.edu

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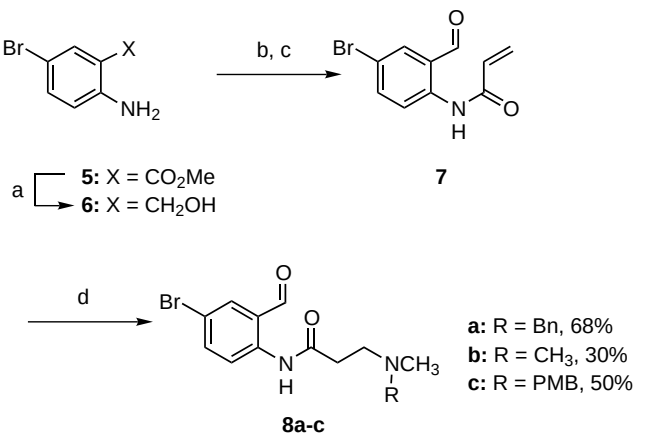
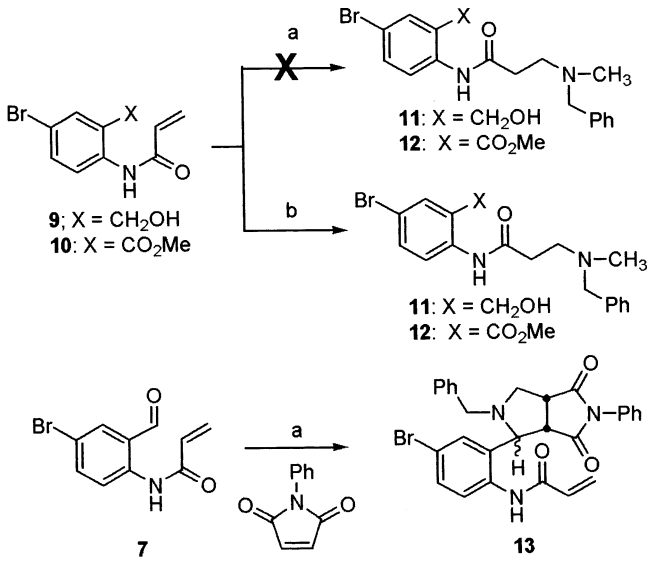
iments suggested that this pathway was independent of the nature of the *N*-substituent (Scheme 1).

The isolation of these amines was completely unexpected as it was erroneously assumed that the electron deficient dipolarophile would readily engage in an intramolecular cycloaddition with the in situ generated azomethine ylide. These observations were particularly surprising when compared to the unactivated systems reported previously by our group, which participate efficiently in the cycloaddition reaction.[2d,l] A series of control experiments were conducted in order to establish the sequence of events leading to these observations. The precursor alcohol **9** and the acrylated ester **10** were subjected to the cycloaddition conditions and it was found that no reaction occurred. On the other hand, both substrates participated in Michael reactions with *N*-methylbenzylamine providing **11** (70%) and **12** (75%), respectively, suggesting that the decarboxylation occurred prior to conjugate addition and that the aldehyde moiety was critical. The benzaldehyde derivative **7** participated in Michael reactions with both *N*-methylbenzylamine and dimethylamine. Taken in combination, these results suggested that the azomethine ylide was indeed forming, but undergoing protonation and hydrolysis prior to cycloaddition. The hydrolysis product, an *N*-methylalkylamine, then adds in a Michael fashion to **7**. Support for this thesis was obtained by running the reaction in the presence of *N*-phenylmaleimide (10 equiv.) when the anticipated intermolecular cycloadduct **13** was obtained in 19% yield as a 3:2 mixture of stereoisomers (Scheme 2).

It has been demonstrated previously that intramolecular reactions involving unsubstituted amides can be retarded as a result of low populations of the reactive conformation.[5] However, this problem can often be circumvented by placing additional substituents on nitrogen, therefore this approach was explored as a means to access compound **4**.[6]

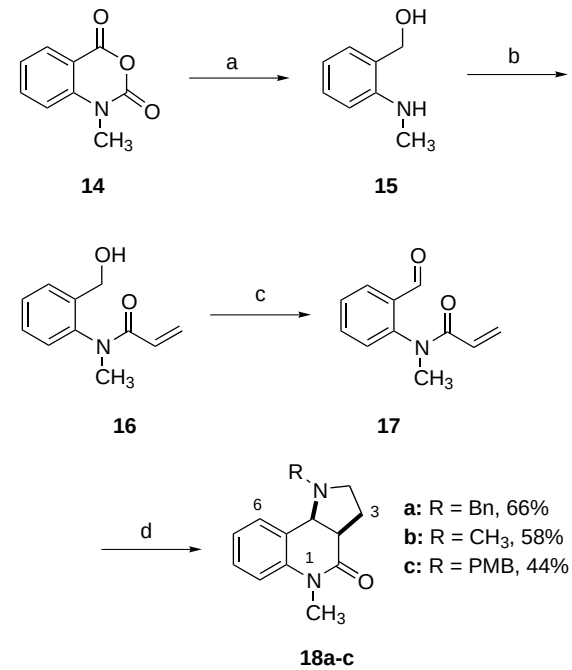



**Scheme 1.** *Reagents and conditions*: (a) $LiAlH_4$, THF, 0°C, 93%. (b) $H_2C$=CHCOCl, $Et_2O$, 43%. (c) $MnO_2$, acetone, 45%. (d) $RNHCH_2CO_2H$·HCl (R = Bn, PMB) or $CH_3NHCH_2CO_2H$, $Et_3N$, PhH, reflux.




**Scheme 2.** *Reagents and conditions*: (a) $BnNHCH_2CO_2H$·HCl, $Et_3N$, PhH, reflux. (b) $BnNHCH_3$, $Et_3N$, PhH, reflux.

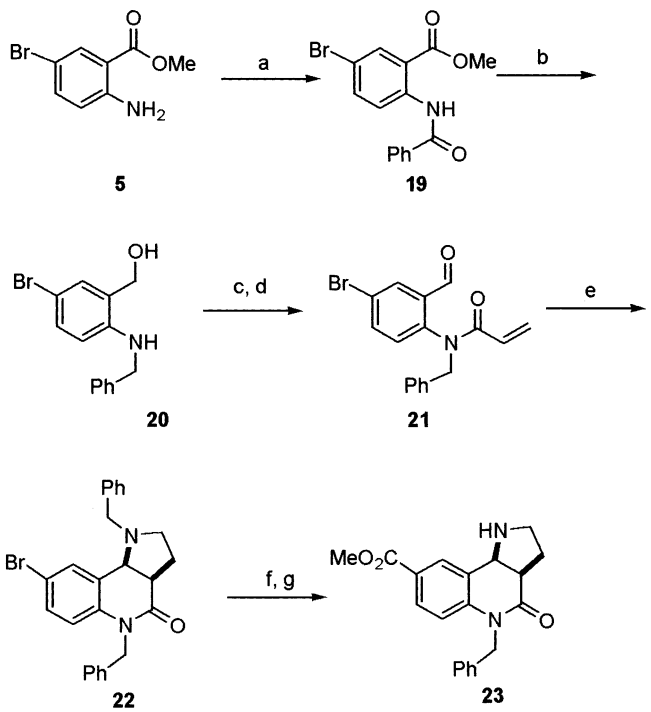
Inititially, attempts were made to alkylate **7** directly with MeI, however, these experiments were unsuccessful, therefore *N*-methyl isatoic anhydride was employed as starting material. Reduction with $LiAlH_4$ provided the known amino alcohol,[7] which was then acylated with acroyl chloride according to the protocol of Heaney and co-workers, providing **16** in good yield (Scheme 3).[7] $MnO_2$ oxidation then provided the required acrylamide in reasonable overall yield.[8] When this substrate was subjected to the cycloaddition reac-




**Scheme 3.** *Reagents and conditions*: (a) $LiAlH_4$, THF, 0°C→rt, 90%. (b) $H_2C$=CHCOCl, $CH_2Cl_2$, $NaHCO_3$, 0°C, 96%. (c) $MnO_2$, $CH_2Cl_2$, 88%. (d) $RNHCH_2CO_2H$·HCl (R = Bn, PMB) or $CH_3NHCH_2CO_2H$, $Et_3N$, $PhCH_3$ (R = Bn, $CH_3$) or DMF (R = PMB), reflux.

tion with *N*-benzyl glycine·HCl in refluxing toluene, we were delighted to find that it had undergone the desired cycloaddition to provide the *cis* pyrroloquinolone **18a** in 66% yield. In addition to the *cis* fused pyrroloquinolone ($J_{2a,5a}=5.5$ Hz), a small quantity of the *trans* product ($J_{2a,5a}=13.8$ Hz), ca. 5% was isolated.[9] Similarly, with sarcosine and *N*-(*p*-methoxybenzyl)glycine·HCl, *cis* pyrroloquinolones **18b** and **c** were obtained in 58 and 44% yields, respectively.[10]

In order to establish whether this approach might be viable en route to the *Martinella* alkaloids, the *N*-benzyl acrylamide derivative was constructed through a largely similar sequence of reactions to those previously employed. Thus, benzoylation of anthranilate derivative **5** gave **19**, which was reduced efficiently to provide the *N*-benzyl alcohol **20**.[11] Acroylation and oxidation afforded the cyclization substrate **21**. When **21** was subjected to the cycloaddition reaction in toluene at reflux, the desired *cis* pyrroloquinolone **22** was obtained in 51% yield. The H5a benzylic proton appeared as a doublet in the $^1$H NMR spectrum, with a coupling constant of 5.0 Hz, which suggested that the ring fusion was *cis*. This assignment was subsequently confirmed through an X-ray structure determination on this adduct, which unequivocally demonstrated that the pyrrole–quinoline ring fusion was *cis*. In addition to the major *cis* adduct, a small quantity (7%) of the *trans* isomer was isolated ($J_{2a,5a}=13.8$ Hz).[12] This assignment was confirmed independently through X-ray crystallography. The bromine substituent was converted via a Pd-catalyzed carbonylation into a carboxymethyl moiety,[13] followed by a chemoselective removal of the pyrrole benzyl group to provide the polar product in 72% yield for two steps (Scheme 4).




**Scheme 4.** *Reagents and conditions*: (a) BzCl, $NaHCO_3$, $CH_2Cl_2$, 95%. (b) $LiAlH_4$, THF, 0°C, 93%. (c) $H_2C$=CHCOCl, $CH_2Cl_2$, $NaHCO_3$, 89%. (d) $MnO_2$, $CH_2Cl_2$, 85%. (e) $BnNHCH_2CO_2H$·HCl, $Et_3N$, $PhCH_3$, reflux, 51% (*cis*). (f) $Pd(OAc)_2$, $PPh_3$, 75 psi CO, MeOH, NaOAc, DMF, 110°C, 76%. (g) $Pd(OH)_2$, $H_2$, MeOH, HCl, 95%.

In summary, a short, stereocontrolled intramolecular cycloaddition approach to pyrrolo[3,2-*c*]quinol-2-ones has been investigated, providing adducts that can be readily functionalized and that should be suitable for elaboration into the *Martinella* alkaloids and/or congeners. Critical to the success of this cycloaddition is the need for *N*-substitution on the acrylamide precursors.

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8. It was found that good yields for this oxidation were obtained on small scales (0.3 mmol) but on larger scales (8.2 mmol) the yield diminished to 55%.
9. We were not able to unequivocally establish the stereochemistry through NOE experiments since the signal due to H2a was obscured by another absorption. However, the magnitude of the coupling constant is consistent with that found for other *cis* pyrroloquinolines ($J=4.0$–$8.3$ Hz) and in particular with that reported by Gurjar ($J=6.6$–$6.8$ Hz) for related pyrroloquinolones (see Ref. 2a).
10. The corresponding *trans* isomers were isolated in 4% yield.
11. Bhalay, G.; Blaney, P.; Palmer, V. H.; Baxter, A. D. *Tetrahedron Lett*. **1997**, *38*, 8375.
12. We believe that the formation of *cis* and *trans* isomers is as kinetic phenomenon since subjection of either isomer to the reaction conditions does not result in their interconversion.
13. Unlike the carbonylations that we had performed in the pyrroloquinoline series (see Ref. 2l), we found that the yield was much lower. This was due to the formation of **22** via a base-induced retro Michael reaction.