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Three-component couplings for the synthesis of pyrroloquinoxalinones by azomethine ylide 1,3-dipolar cycloaddition chemistry

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ABSTRACT

1-Methyl-3,4-dihydroquinoxalin-2(1*H*)-one was heated with a range of aldehydes to generate intermediate azomethine ylides which underwent [3 + 2] cycloaddition reactions with *N*-methyl or *N*-phenylmaleimide to give substituted tetrahydropyrroloquinoxalinones. Only one (racemic) stereoisomer was formed in each case and the stereochemical outcome was verified by single crystal X-ray analysis. The products from this multicomponent reaction could be oxidised with DDQ to the pyrroloquinoxalinones.

Introduction

Cycloaddition reactions using azomethine ylides have been used widely to synthesise organic molecules containing pyrrolidine and pyrrole rings [1–4]. There are many ways to prepare the intermediate azomethine ylides and one of the most simple involves the reaction between a secondary amine and an aldehyde. If the amine contains an electron withdrawing group in the α-position, such as an ester, then the resulting iminium ion can be deprotonated to give an azomethine ylide [5–16]. As an alternative to an ester, a lactone can be used as a stabilising group to generate azomethine ylides, which has allowed access to a variety of different polycyclic compounds [17–19]. In contrast, electron withdrawing amides or lactams are relatively uncommon as stabilising groups for intermediate azomethine ylides [20–25]. Six-membered lactams such as piperazinones are important functional groups which have a large number of applications, especially in medicinal chemistry [26–28]. However piperazinones and their benzo-fused derivatives (dihydroquinoxalinones, **1**) have not, to the best of our knowledge, been used to form azomethine ylides for dipolar cycloaddition reactions. Cycloadducts **2** have an interesting tricyclic structure, where a pyrrolidine is fused with a dihydroquinoxalinone (Scheme 1).

The pyrroloquinoxalinone structure has been synthesised previously using cyclization reactions [29–36]. However, [3 + 2] cycloaddition reactions could provide a very efficient route to these compounds, which have the potential for significant biologically activity. Similar structures have been found to have biological relevance as, for example, GABA/benzodiazepine receptor ligands, 5-HT_3 receptor agonists, or vascular smooth muscle relaxants (Fig. 1) [37–40]. Herein, we highlight the use of 3,4-dihydroquinoxalin-2(1*H*)-one **1** in [3 + 2] cycloaddition reactions to generate a series of novel tetracyclic compounds based on this core ring system.

Results and discussion

We began by synthesising the dihydroquinoxalinone **1** using a known procedure (see Supplementary Data) [41]. With this compound in hand we studied the use of conditions similar to those reported by Siedel and co-workers [42] to try to effect the desired cycloaddition reaction (Scheme 2). Heating dihydroquinoxalinone **1** with benzaldehyde, 4 Å molecular sieves (MS), benzoic acid and *N*-methylmaleimide in toluene failed to give the desired cycloaddition product and returned only recovered starting materials. Substituting benzoic acid for the stronger acid camphorsulfonic acid (CSA) gave a similar result, but oxidised compound **3** was isolated instead of compound **1**. It was clear that oxidation of the starting material was interfering with the desired reaction [43]. To investigate the oxidation reaction further, dihydroquinoxalinone **1** was heated at reflux in toluene with 10 mol% CSA in the absence of aldehyde or maleimide. Analysis of the reaction mixture after 17 h by ^{1}H NMR spectroscopy indicated a mixture of dihydroquinoxalinone **1** and its oxidised form **3** in a 1:1.2 ratio. In contrast, by carrying out the same reaction under an argon atmosphere, ^{1}H

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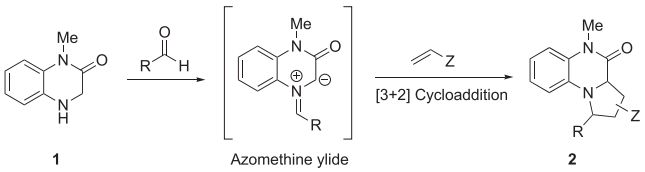


Scheme 1. General cycloaddition reaction under study.

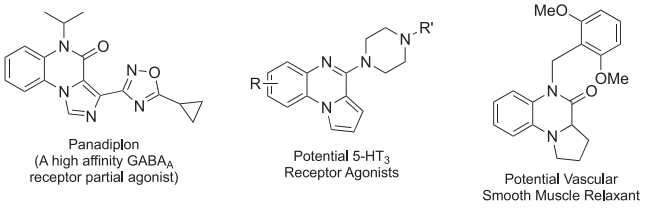
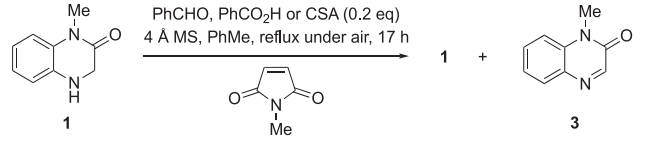


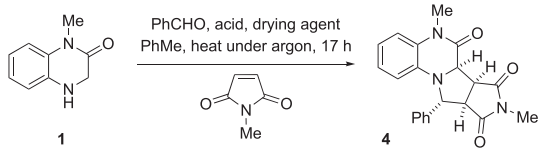
Figure 1. Bioactive tricyclic quinoxalin(on)es.



Scheme 2. Initial attempted cycloaddition reaction.

NMR spectroscopy of the reaction mixture indicated that no oxidised material **3** had been formed.

We therefore repeated the cycloaddition reaction under an inert atmosphere and were pleased to find that the desired cycloadduct **4** was formed as a single racemic diastereoisomer in moderate yield (Scheme 3). The reaction conditions were optimised as shown in Table 1. Initially increasing the amount of CSA caused an increase in the yield of cycloadduct **4**, with a maximum yield of 57% being obtained when 15 mol% of CSA was added (Entry 3). Decreasing the reaction temperature caused a decrease in the yield of cycloadduct **4** (Entry 5). Although the addition of the drying agent $MgSO_4$ did not affect the yield (Entry 6), the use of 4 Å molecular sieves was beneficial (Entry 7). Changing the molar ratio of dihydroquinoxalinone **1** and benzaldehyde gave variable yields of



Scheme 3. Cycloaddition to give tetracycle **4**.

Table 1
Optimization of the cycloaddition in Scheme 3.

Entry	Conditions	Yield **4** (%)
1	2 eq. **1**, no acid, 110 °C, no drying agent	0
2	2 eq. **1**, 10 mol% CSA, 110 °C, no drying agent	47
3	2 eq. **1**, 15 mol% CSA, 110 °C, no drying agent	57
4	2 eq. **1**, 20 mol% CSA, 110 °C, no drying agent	49
5	2 eq. **1**, 15 mol% CSA, 90 °C, no drying agent	40
6	2 eq. **1**, 15 mol% CSA, 110 °C, $MgSO_4$	48
7	2 eq. **1**, 15 mol% CSA, 110 °C, 4 Å MS	63
8	1.5 eq. **1**, 15 mol% CSA, 110 °C, 4 Å MS	**69**
9	1 eq. **1**, 15 mol% CSA, 110 °C, 4 Å MS	54
10	1.5 eq. PhCHO, 15 mol% CSA, 110 °C, 4 Å MS	25
11	1.5 eq. **1**, 15 mol% $PhCO_2H$, 110 °C, 4 Å MS	32

cycloadduct **4** (Entries 8–10) with the best result being obtained when using 1.5 eq. dihydroquinoxalinone **1** and 1 eq. benzaldehyde (Entry 8). However, it was possible to obtain a good yield with 1 eq. of each of component: **1**, PhCHO, and *N*-methylmaleimide (Entry 9). Finally, when the acid was changed from CSA to benzoic acid there was a decrease in the yield (Entry 11).

The stereochemistry of compound **4** was confirmed by single crystal X-ray crystallography (Fig. 2), which showed a *trans* configuration between the protons α to the amine nitrogen atom and therefore that the [3 + 2] cycloaddition occurs with the S-shaped ylide (assuming a concerted process, although it is possible that the reaction is stepwise). The dipolarophile *N*-methyl maleimide approaches *trans* to the phenyl group (*endo* selectivity).

Using the optimised conditions, we then explored the substrate scope of the reaction. By varying the aldehyde, we were able to obtain a range of different cycloadducts **5**–**8** (Scheme 4). The reaction was successful with both electron-poor (4-nitro) and electron-rich (4-methoxy) benzaldehydes, although the yield of cycloadduct **6** in the latter case was low. It was pleasing to find that the reaction was successful with a heteroaryl group (thiophenyl) and with the non-aromatic aldehyde cyclohexane-carbaldehyde, which gave the desired cycloadducts **7** and **8** respectively. In all cases for products **5**–**8** only a single stereoisomer was isolated and each had very similar coupling constants in the ^{1}H NMR spectra, suggesting that they all have the same relative stereochemistry as determined for adduct **4**.

We then attempted to expand the scope of the dipolarophile by testing different electron-poor alkenes. However mostly starting materials and no desired cycloadducts were isolated on heating amine **1** and PhCHO with dimethyl fumarate, methyl *trans*-cinnamate, diethyl acetylenedicarboxylate, or benzylidenemalononitrile.

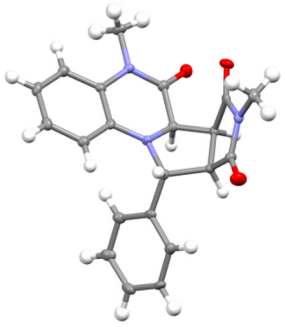
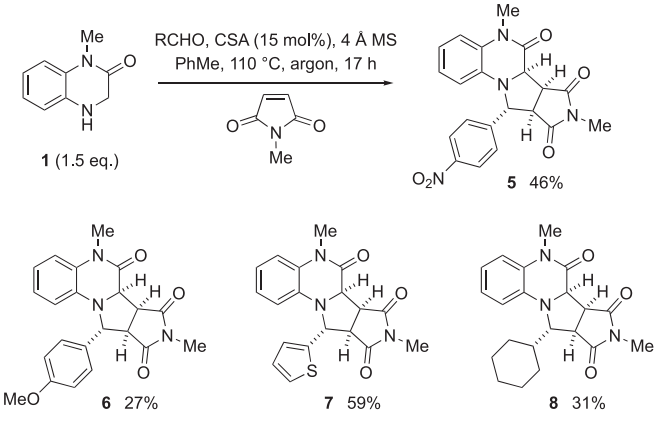
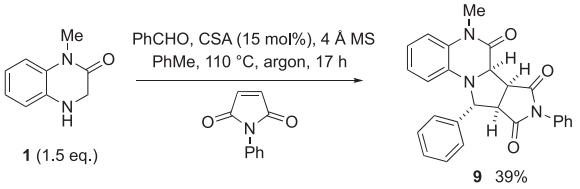


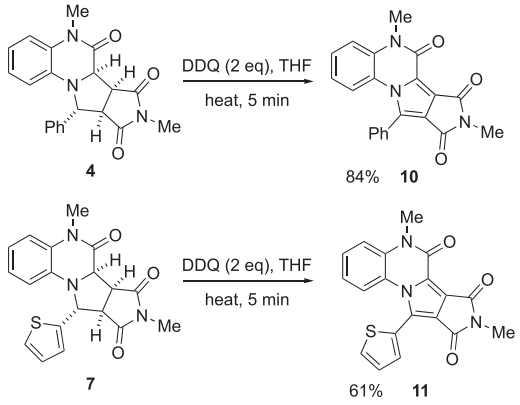
Figure 2. Single crystal X-ray structure for (±)-**4**.



Scheme 4. Exploring the scope of the aldehyde RCHO.



Scheme 5. Cycloaddition with *N*-phenylmaleimide.



Scheme 6. Oxidation of the cycloadducts.

The reaction was successful with *N*-phenylmaleimide to give cycloadduct **9** in 39% yield (Scheme 5).

Finally, the scope of chemistry was extended by oxidation of cycloadducts **4** and **7** using 4,5-dichloro-3,6-dioxo-1,4-cyclohexadiene-1,2-dicarbonitrile (DDQ). This resulted in the formation of compounds **10** and **11**, respectively, in good yields (Scheme 6).

Conclusion

In conclusion, we have demonstrated a successful and simple protocol for a multicomponent coupling reaction involving azomethine ylide dipolar cycloaddition chemistry from dihydroquinoxalinone **1** and a variety of aldehydes. The scope of the dipolarophile needs further study but the chemistry allows access to novel heterocyclic products as single stereoisomers. The strategy provides a way to prepare libraries of compounds based on the pyrroloquinoxalinone core for biological screening.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data (Experimental procedures, spectroscopic and X-ray data (CCDC 1939356 for compound **4**) and copies of NMR spectra) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151023.

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