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Divergent synthesis of (quinoxalin-2-yl)-1,3-oxazines and pyrimido[1,6-*a*]quinoxalines *via* the cycloaddition reaction of acyl(quinoxalinyl) ketenes

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ABSTRACT

A facile synthetic approach towards two distinct quinoxaline-based heterocyclic scaffolds has been developed from the cycloaddition of acyl(quinoxalinyl)ketenes with carbodiimides. The described reaction represents the first example of a divergent synthesis based on acyl(quinoxalinyl)ketenes providing (quinoxalin-2-yl)-1,3-oxazines or pyrimido[1,6-*a*]quinoxalines depending on the type of the acyl substituent in the ketenes. The key reactants, acyl(quinoxalinyl)ketenes, are generated *in situ via* the thermal decarbonylation of readily available pyrroloquinoxaline oxo-derivatives. The proposed diversity-oriented synthesis provides facile access to a library of skeletally diverse pharmaceutically interesting quinoxaline-based heterocycles from inexpensive reagents.

Diversity-oriented synthesis (DOS) is a powerful strategy in modern drug discovery [1]. The most tunable and predictable DOS strategies for small molecule library design are based on the known properties of certain functional groups introduced in sets of reactants in different combinations [2]. DOS with an emphasis on skeletal diversity provides an opportunity to screen wider chemical space creating diverse compound libraries from a limited set of reagents, which reduces the cost and facilitates the development of new drugs. In this way, the search and investigation of reactivity for new building blocks bearing several functional groups is essential for expansion of DOS scope.

Recently, compounds bearing a quinoxalin-2(1*H*)-one moiety were found to exhibit a wide range of biological activities [3]. For example, among them were found 5-HT2C agonists [3a], antihypoxants [3b], antiprotozoan [3c] and cytotoxic [3d] agents (Fig. 1).

Acyl(imidoyl)ketenes are highly reactive compounds bearing a forked diene fragment consisting of a C=C bond conjugated with geminal C=O and C=N fragments. This structural feature makes them appealing candidates for the development of DOS with an emphasis on skeletal diversity. Additionally, the presence of the C=N bond in acyl(imidoyl)ketenes enables the introduction of a pharmaceutically important quinoxaline fragment (in particular, a quinoxalin-2(1*H*)-one moiety), and the resulting acyl(quinoxalinyl)ketenes can be easily modified at the O=C=C–C=N or O=C=C–C=O motifs.

Acyl(quinoxalinyl)ketenes react selectively either as O=C=C–C=O [4] or as O=C=C–C=N [5] dienes in reactions with various dienophiles (Scheme 1). The regioselectivity of the reaction depends on the type of dienophiles and substituents at the C^3 atom of the quinoxaline moiety of acyl(quinoxalinyl)ketenes. To the best of our knowledge there are no reported examples of the involvement of acyl(quinoxalinyl)ketenes in a divergent cycloaddition reaction with a single class of dienophiles.

Herein, we report the first example of a divergent cycloaddition reaction of acyl(quinoxalinyl)ketenes (bearing a pharmaceutically valuable quinoxalin-2(1*H*)-one moiety) resulting in either (quinoxalin-2-yl)-1,3-oxazines or pyrimido[1,6-*a*]quinoxalines (Scheme 1).

Acyl(quinoxalinyl)ketenes **1** are known to react with dienophiles exclusively at the O=C=C–C=O system (Scheme 1) [4]. At the same time, we previously described the reaction of acyl(quinoxalinyl)ketenes **2** with Schiff bases affording exclusively the products of cycloaddition at the O=C=C–C=N system (Scheme 1) [5]. Considering these two facts, we envisioned that there might be reagents that can react with acyl(quinoxalinyl)ketenes **2** both at the oxo-diene and aza-diene fragments under certain conditions.

The acyl(quinoxalinyl)ketenes **2** of interest are highly reactive compounds which are most commonly generated *in situ via* the

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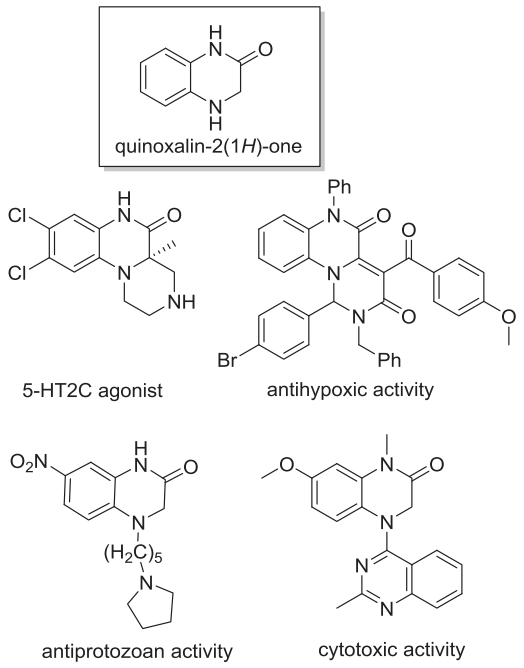
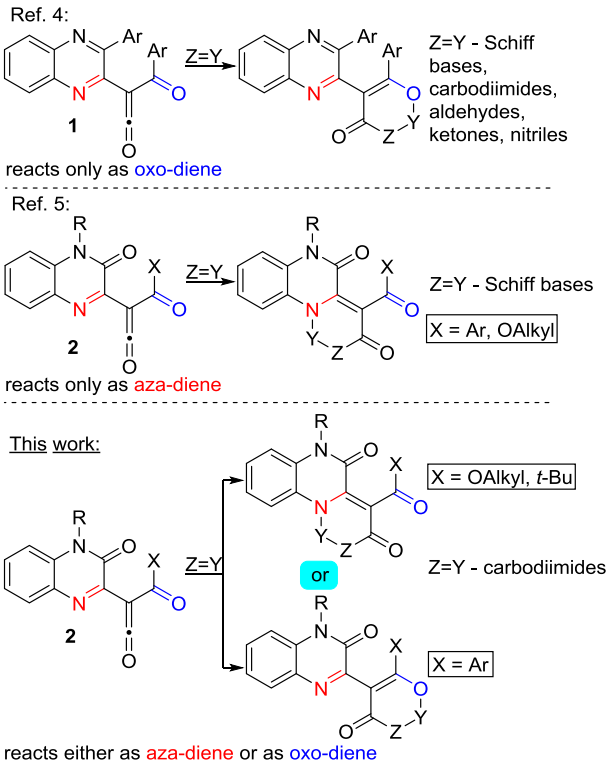


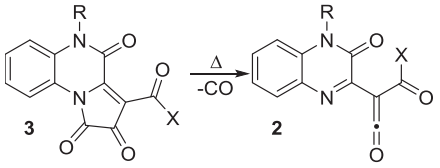
Fig. 1. Selected examples of skeletally diverse biologically active quinoxalin-2(1*H*)-one based compounds.



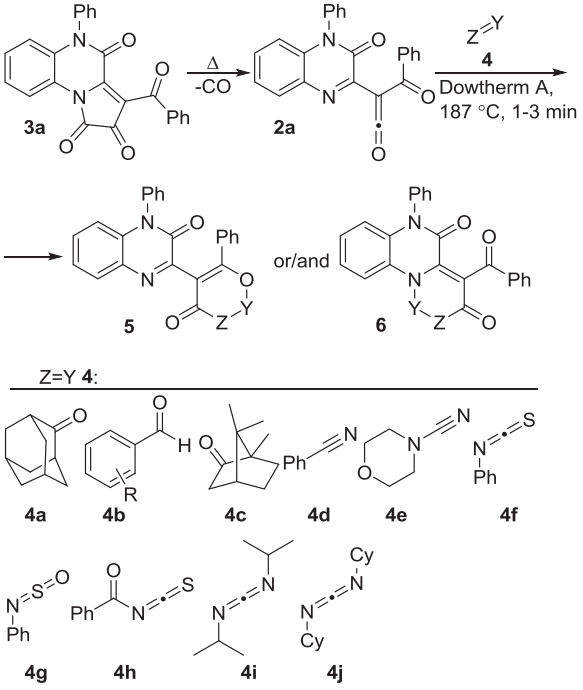
Scheme 1. Directions of cycloaddition reactions of acyl(quinoxalinyl)ketenes with dienophiles.

thermal decarbonylation of pyrroloquinoxalinetriones **3** (Scheme 2) [5,6].

To start with, we examined the reaction of pyrroloquinoxalinetrione **3a** with various dienophiles (Scheme 3), paying special attention to those described to react with ketenes **1** at the oxo-diene motif [4].



Scheme 2. Thermal decarbonylation of pyrroloquinoxalinetriones **3**.



Scheme 3. Dienophiles **4** scope examination for the reaction with pyrroloquinoxalinetrione **3a** under thermal decarbonylation conditions.

Mixtures of equimolar amounts of pyrroloquinoxalinetrione **3a** with various dienophiles **4a–j** (Scheme 3) were heated in Dowtherm A at 187 °C (onset decarbonylation temperature of **3a** [5]) for 1–3 min, and the obtained reaction mixtures were examined by UPLC-MS.

The reaction of ketene **2a** with adamantanone **4a** gave adducts **5** or **6** in only trace amounts. Aromatic aldehyde **4b** did not give any detectable adducts. These outcomes could be explained by the thermal instability of possible adducts which decomposed rapidly at such a high temperature. Our efforts to increase the yields of the desired adducts by reducing the reaction temperature were unsuccessful.

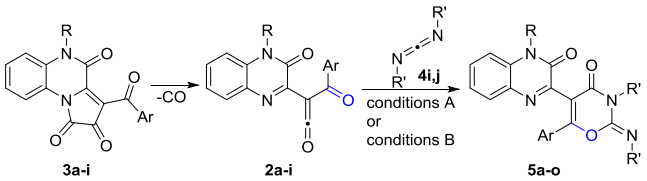
Camphor **4c** did not afford the desired adducts **5** or **6**, and instead a complex mixture of adducts of compound **3a** with camphor was detected. Possibly, the reaction with camphor **4c** proceeded in a similar way as described for the reaction of pyrroloquinoxalinetriones **3** with cyclohexanone [7].

Benzonitrile **4d** also did not give any detectable adducts. However, morpholine-4-carbonitrile **4e** was found to react with compound **3a** before its thermal decarbonylation, and unspecified adducts of compound **3a** with morpholine-4-carbonitrile were detected as the major components of this reaction mixture.

Phenyl isothiocyanate **4f**, *N*-thionylaniline **4g** and benzoyl isothiocyanate **4h** also did not give any detectable adducts.

Finally, the reactions of compound **3a** and carbodiimides (dicyclohexylcarbodiimide (DCC) **4i**, diisoproylcarbodiimide (DIC) **4j**) gave the desired adducts **5a**,**b** (Table 1) in acceptable yields (**4i**,

Table 1
Substrate scope examination for the synthesis of (quinoxalin-2-yl)-1,3-oxazines **5**.



Entry	R	Ar	R′	5	Yield[a] (%)
1	Ph	Ph	Cy	**5a**	82[b]
2	Ph	Ph	*i*-Pr	**5b** (CCDC 1935937)	61[c]
3	Ph	$C_6H_4NO_2$-4	Cy	**5c**	73[b]
4	Ph	C_6H_4Cl-4	Cy	**5d**	79[b]
5	Ph	C_6H_4OMe-4	Cy	**5e**	81[b]
6	Ph	C_6H_4Cl-4	*i*-Pr	**5f**	69[c]
7	Me	Ph	Cy	**5g**	73[b]
8	Me	C_6H_4Cl-4	Cy	**5h**	77[b]
9	Me	C_6H_4OMe-4	Cy	**5i**	80[b]
10	Ph	C_6H_4OMe-4	*i*-Pr	**5j** (CCDC 1935941)	61[c]
11	Ph	$C_6H_4NO_2$-4	*i*-Pr	**5k** (CCDC 1935940)	64[c]
12	Me	Ph	*i*-Pr	**5l**	68[c]
13	Me	C_6H_4Cl-4	*i*-Pr	**5m**	71[c]
14	Me	C_6H_4OEt-4	Cy	**5n**	78[b]
15	Me	C_6H_4Me-4	Cy	**5o**	79[b]

[a] Isolated yield.
[b] Conditions A: decarbonylation onset temperature of **3**, 1–3 min, solvent-free, 10% excess of carbodiimide **4** (for DCC **4i**).
[c] Conditions B: decarbonylation onset temperature of **3**, 1–3 min, Dowtherm A, 60% excess of carbodiimide **4** (for DIC **4j**).

78% yield and **4j**, 46% yield). It should be noted that compounds **5a, b** were formed as the sole regioisomers, and no signals of regioisomeric cycloadducts **6** (Scheme 3) of ketene **2a** with carbodiimides **4i,j** were observed by UPLC-MS.

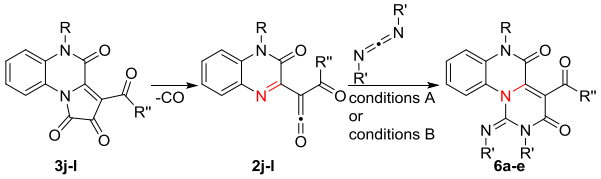
To improve the discovered reaction conditions, we tested this reaction under solvent-free conditions, as proposed earlier for the trapping of ketenes **2** by Schiff bases [5]. For this purpose, equimolar amounts of pyrroloquinoxalinetrione **3a** and carbodiimides **4i,j** were thoroughly homogenized and compacted, and then the obtained mixtures were heated at 187 °C (onset decarbonylation temperature of **3a** [5]) for 1–3 min, and the reaction mixtures were examined by UPLC-MS. As a result, we observed that the reaction with DCC **4i** proceeded well under solvent-free conditions (**5a**, 80% yield), and the reaction with DIC **4j** showed unsatisfactory results (**5b**, 16% yield). Such a trend could be explained by the relatively low boiling point of DIC (145–148 °C) which had evaporated prior to the onset of decarbonylation. Increasing the DIC amount to a twofold excess did not significantly improve the reaction (**5b**, 27%). Thus, we established that the solvent-free protocol can be implemented with DCC **4i** and is unsuitable for DIC **4j**.

Having optimized the reaction conditions, we screened the pyrroloquinoxalinetriones **3a–i** (bearing an aroyl group) scope to afford the desired compounds **5a–o** (Table 1). As a result, we found that the reactions of pyrroloquinoxalinetriones **3a–i** proceeded well to form the desired (quinoxalin-2-yl)-1,3-oxazines **5a–o** regardless of the aroyl group substituent.

To implement the alternative direction for the cycloaddition of carbodiimides **4i,j** to ketenes **2**, pyrroloquinoxalinetriones **3j,k** bearing alkoxycarbonyl groups (difficult to enolize) were reacted with DCC **4i** and DIC **4j**. As expected, the products were pyrimido[1,6-*a*]quinoxalines **6a–c** (Table 2).

Interestingly, the pivaloyl group bearing pyrroloquinoxalinetrione **3 l** reacted with carbodiimides **4i,j** under thermal decarbonylation conditions to form pyrimido[1,6-*a*]quinoxalines **6d,e** (Table 2) instead of the expected (quinoxalin-2-yl)-1,3-oxazines. This can be explained by steric hindrance induced by the *tert*-butyl group or

Table 2
Substrate scope examination for the synthesis of pyrimido[1,6-*a*]quinoxalines **6**.



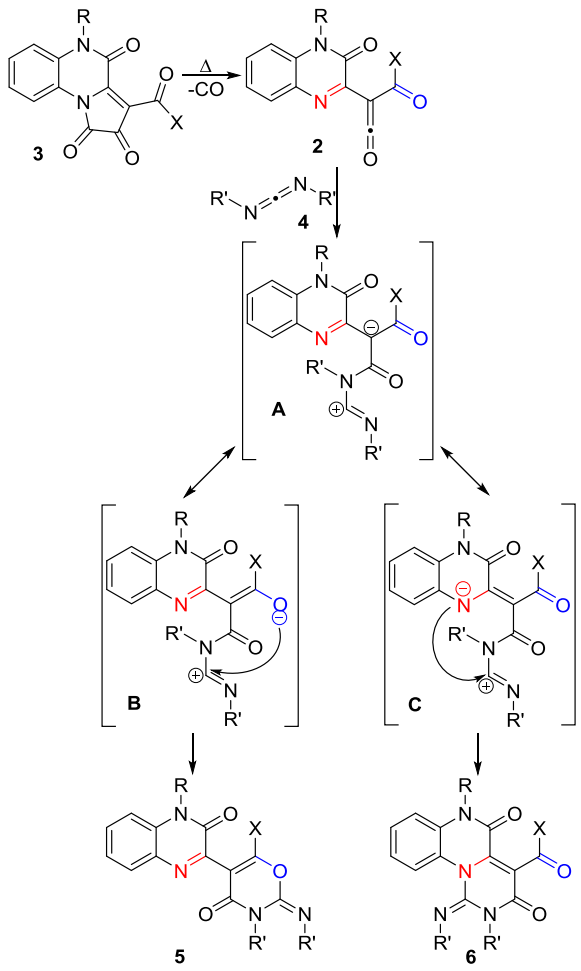
Entry	R	R′	6	Yield[a] (%)
1	OEt	Cy	**6a**	73[b]
2	OMe	*i*-Pr	**6b**	61[c]
3	OMe	Cy	**6c** (CCDC 1935938)	76[b]
4	*t*-Bu	Cy	**6d** (CCDC 1935939)	76[b]
5	*t*-Bu	*i*-Pr	**6e**	51[c]

[a] Isolated yield.
[b] Conditions A: decarbonylation onset temperature of **3**, 1–3 min, solvent-free, 10% excess of carbodiimide **4** (for DCC **4i**).
[c] Conditions B: decarbonylation onset temperature of **3**, 1–3 min, Dowtherm A, 60% excess of carbodiimide **4** (for DIC **4j**).

poor enolization of the pivaloyl carbonyl group due to the strong electron donor effect of the *tert*-butyl substituent.

Notably, compounds **6a–e** were also formed as sole regioisomers, and no signals of regioisomeric cycloadducts **5** were observed by UPLC-MS (Scheme 3).

We assume that the divergent formation of (quinoxalin-2-yl)-1,3-oxazines **5** or pyrimido[1,6-*a*]quinoxalines **6** proceeded according to Scheme 4. First, pyrroloquinoxalinetriones **3** underwent thermal decarbonylation affording *in situ* generation of acyl (quinoxalinyl)ketenes **2**. Ketenes **2** reacted with carbodiimides **4** to form zwitterionic intermediates **A**. In the case of aroyl substituents, zwitterions **A** underwent charge-controlled intramolecular cyclization at the readily enolizable carbonyl group of the aroyl



Scheme 4. Plausible pathway for the reaction of acyl(quinoxalinyl)ketenes **2** with carbodiimides **4**.

substituent. Conversely, alkoxycarbonyl/pivaloyl bearing zwitterions **A** underwent intramolecular cyclization at the enamino motif because its enolized resonance structure **B** is unfavorable.

In conclusion, we have developed a divergent synthetic methodology towards two distinct quinoxaline-based heterocycles based on the substituent controlled cycloaddition reaction of acyl(quinoxalinyl)ketenes with carbodiimides. Acyl(quinoxalinyl)ketenes were generated *in situ* as a result of the thermal decarbonylation reaction of pyrroloquinoxalinetriones. In the case of aroyl substituted acyl(quinoxalinyl)ketenes, the O=C=C–C=O system underwent the cycloaddition reaction, and (quinoxalin-2-yl)-1,3-oxazines were obtained as the sole products. Involvement of alkoxycarbonyl or pivaloyl substituted acyl(quinoxalinyl)ketenes led to the exclusive formation of pyrimido[1,6-*a*]quinoxalines, the products of cycloaddition at the O=C=C–C=N system. Our study is the first example of a divergent cycloaddition reaction of acyl(quinoxalinyl)ketenes resulting in either (quinoxalin-2-yl)-1,3-oxazines or pyrimido[1,6-*a*]quinoxalines formation. The proposed strategy provides facile access to a library of skeletally diverse pharmaceutically interesting quinoxaline-based heterocycles from inexpensive reagents.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151088. These data include MOL files and InChiKeys of the most important compounds described in this article.

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