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Regioselective synthesis of 2-iminooxazinones from dioxinones and carbodiimides

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ABSTRACT

Iminooxazinones are readily formed via microwave heating of dioxinones in the presence of carbodiimides. Unsymmetrically substituted carbodiimides generally react with high or complete regioselectivity, allowing for assembly of the target ring systems with full control of substitution pattern under convenient conditions.

Scaffolds based on nitrogen-containing heterocycles are common in many classes of bioactive substances, such as pharmaceuticals and agricultural chemicals. Methods for convergent generation of such skeletons in a single step are especially attractive, both from a step-economy standpoint and as an approach for the preparation of structurally diverse compound libraries. Oxidized oxazine derivatives such as amino- and iminooxazinones (Fig. 1) possess heteroatom-rich structures with multiple attachment points for variable side-chains and several hydrogen bond acceptors and/or donors. Compounds with these substructures have been described, pertaining to anti-cancer, analgesic, and fungicidal activities.[1] Moreover, iminooxazinones are versatile intermediates in the construction of other heterocyclic classes, such as 4-oxooxazinones or uracils.[2]

Iminooxazinones can be prepared in one step from cycloaddition or cyclocondensation of simple carbodiimides with allene-containing carboxylic acids,[3] salicylic acids,[4] or acylketenes derived from precursors such as diketenes,[2] diazocarbonyls,[5] furandiones,[6] or dioxinones.[7] Persistent acylketenes also undergo this process.[8] Acylketenes are generated in situ from malonic acid monoesters in the presence of DCC, and in one case this intermediate was trapped in a subsequent cycloaddition with a second equivalent of the carbodiimide.[9] We encountered a similar result during the preparation of β-ketoester **2** from ketoacid **1**, a process that was frequently complicated by the competing formation of iminooxazinone **4a**, especially on attempted scale-up (Scheme 1). This reaction is presumed to proceed through initial DCC-mediated dehydration to give the acylketene intermediate **3a**, followed by

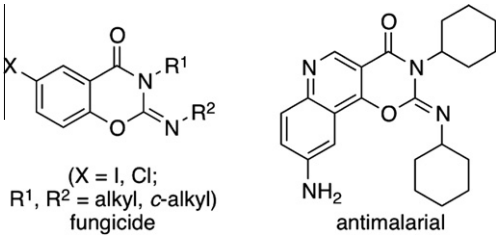
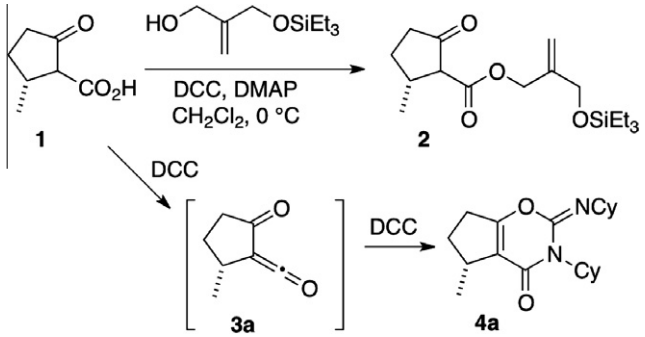


Figure 1. Representative iminooxazinones.



Scheme 1. Formation of iminooxazinone **4a** from **1** and DCC.

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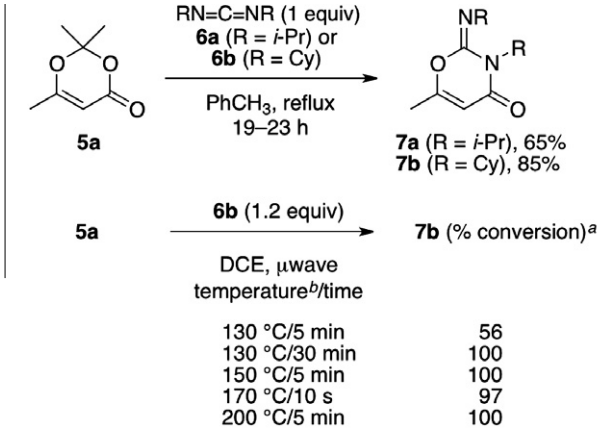


[a] Percent conversion was determined by integration of the C=CH singlets of **5a** and **7b** in the crude ^{1}H NMR spectrum. [b] Reaction temperature was determined through measurement of the vial surface temperature using an infrared sensor, then corrected for internal temperature by the microwave reactor's internal processor using a proprietary algorithm.

Scheme 2. Initial experiments with dioxinone **5a**.

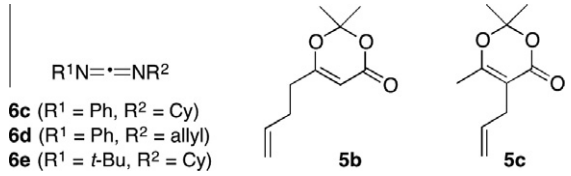


Figure 2. Unsymmetrical substrates.

cycloaddition with a second equivalent of DCC. As noted above, there is ample precedent for the construction of iminooxazinones from simple carbodiimides and ketene equivalents; on the other hand, relatively little is known regarding regiochemical outcomes in cases involving unsymmetrical partners. With this in mind, we set out to prepare a series of unsymmetrical carbodiimides and acylketene precursors and evaluate their cycloaddition behavior. Here we describe the results of this study, including convenient reaction conditions using microwave heating, and complete regioselectivity in the cycloaddition process.

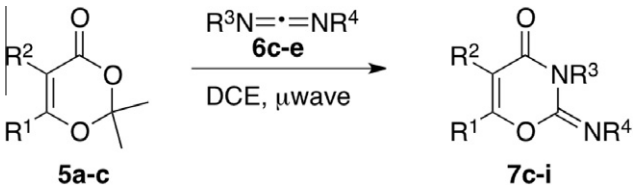
Before addressing the question of regioselectivity, we first sought to develop a procedurally simple method for effecting the cycloaddition to afford the iminooxazinone products. Keto-acid starting materials such as **1** require the use of 2 equiv of carbodiimide: one for dehydration to generate the transient acylketene (with consequent formation of urea by-product), and one to participate in the subsequent cycloaddition process. As noted above, there are several alternative routes to acylketenes, and we were particularly attracted to the dioxinone method,[7] given its procedural simplicity, the innocuous by-product (acetone), and the potential for structural modification of the commercially available 2,2,6-trimethyldioxinone **5a**.

Initial experiments utilized **5a** and either diisopropylcarbodiimide **6a** or dicyclohexylcarbodiimide **6b** (Scheme 2). Extended heating in toluene at reflux furnished known iminooxazinones **7a** [2] and **7b**[7] in good yield, comparable to previously described cases employing dioxinones with either **6b** or diphenylcarbodiimide in xylene or mesitylene at reflux. In an effort to shorten the reaction time, the effect of microwave heating[10] on the reaction with DCC **6b** was investigated on a small scale with % conversion determined via ^{1}H NMR analysis. In the event, 100% conversion was observed after 30 min at 130 °C, while only 5 min was required at 150 °C. Given these results, subsequent preparative scale experiments were carried out with microwave heating at either 150 °C or 200 °C.

Several unsymmetrically substituted carbodiimides[11] were prepared (Fig. 2). Phenyl cyclohexyl carbodiimide **6c** was prepared by the method of Palomo and Mestres via dehydration of the corresponding mixed urea.[11a] The known [11e–g] phenyl allyl carbodiimide **6d** and *t*-butyl cyclohexyl carbodiimide **6e** were prepared using the same method. Regioisomeric allylation products **5b** [12] and **5c** [13] are both available from **5a**, and were prepared by a variation on these procedures.

Using the microwave heating conditions worked out with **5a** and **6b**, dioxinones **5a**–**c** were treated with unsymmetrical carbodiimides **6c**–**e** to afford iminooxazinones **7c**–**i** in moderate to good yields (Table 1). In most cases, reactions were carried out at both 150 °C and 200 °C, and the higher yielding conditions are included in the table. In most cases, the higher temperature furnished **7** in higher yield, though in the case of **5a** and **6c**, a shorter reaction time was required (entry 2). A higher temperature was consistently desirable in the case of more substituted dioxinones **5b** and **5c**, whose expulsion of acetone is slow at 150 °C. With dioxi-

Table 1
Cycloaddition of dioxinones with carbodiimides[a]



Entry	Dioxinone	Carbodiimide	R^1	R^2	R^3	R^4	Iminooxazinone	*T* (°C)	Yield **7**[b] (%)
1	**5a**	**6c**	Me	H	Cy	Ph	**7c**	150	71
2	**5a**	**6c**	Me	H	Cy	Ph	**7c**	200[c]	75
3	**5a**	**6d**	Me	H	Allyl	Ph	**7d**	200	93
4	**5a**	**6e**	Me	H	Cy	*t*-Bu	**7e**	150	82
5[d]	**5b**	**6c**	$(CH_2)_2CH{=}CH_2$	H	Cy	Ph	**7f**	200	75
6[d]	**5b**	**6d**	$(CH_2)_2CH{=}CH_2$	H	Allyl	Ph	**7g**	200	68
7[d]	**5b**	**6e**	$(CH_2)_2CH{=}CH_2$	H	Cy	*t*-Bu	**7h**	200	71
8[d]	**5c**	**6c**	Me	Allyl	Cy	Ph	**7i**	200	42

[a] Standard conditions: Dioxinone **5** (0.22 mmol) and carbodiimide **6** (0.27 mmol) were dissolved in DCE (0.5 mL) in a microwave reaction vial, then subjected to microwave heating at 150 °C or 200 °C for 5 min. Solvent was removed and the crude reaction mixture purified by column chromatography.
[b] Yields given are for isolated material after chromatographic purification, and reflect average values taken from at least two runs.
[c] Reaction time was reduced to 10 s.
[d] Acetone (5 μL, 0.07 mmol) was added to the reaction mixture.

nones **5b** and **5c**, it was found beneficial to include a small amount of added acetone to the reaction mixture to enhance the rate of microwave heating.[14]

Importantly, in all examples only one regioisomer was detected. While regioselectivity has been described in a few early examples involving unsymmetrical reactants,[2] these results indicate a heretofore unappreciated generality of this phenomenon for this transformation. Evidence for the indicated regiochemistry includes the following. In the case of DCC adduct **7b**, a characteristic difference in chemical shift (4.68 vs 3.60 ppm) for the cyclohexyl methine protons was noted (Fig. 3) allowing for tentative determination of the location of the cyclohexyl substituent in adducts derived from **6c** and **6e**. Thus, in the case of **7c**, the single cyclohexyl methine resonance appears at 4.82 ppm, consistent with substitution on the ring nitrogen. Furthermore, a 3-bond HMBC correlation was detected between the cyclohexyl methine proton and the carbonyl carbon (possible for **7c** but not for its hypothetical regioisomer **8c**) and an NOE correlation was observed between the ortho phenyl protons and the methyl protons. Regiochemistry in other cases was assigned by analogy. It should be noted that the NOE correlation mentioned above not only supported the regiochemical assignment, but also strongly suggested a (*Z*) geometry for the exocyclic imino group. This geometry for a C=NPh moiety was also observed in the X-ray crystal structure for diphenylcarbodiimide adduct **7j**,[2b,7,15] and likely arises from avoidance of unfavorable steric interactions between the two nitrogen substituents.

The mechanism of the cycloaddition process remains uncertain at this time. Two mechanistic extremes are concerted [4+2]-cycloaddition and stepwise nucleophilic attack by one nitrogen atom at the electrophilic ketene carbon, followed by electrocyclic ring-closure (Scheme 3). In the case of alkyl aryl carbodiimides **6c** and **6d**, the alkyl-substituted nitrogen is consistently incorporated into the ring (R^3). Preferential bonding between this more nucleophilic nitrogen and the former ketene carbon atom suggests that the cycloaddition may proceed with a significant polar component. On the other hand, the difference in relative nucleophilicity of the two carbodiimide nitrogens of **6e** is likely to be negligible, and selective placement of the *t*-butyl substituent on the exocyclic imino nitrogen may result from avoidance of unfavorable steric interactions in the transition state for addition. Reaction of 1-*t*-butyl-3-phenylcarbodiimide[11f,g,16] would provide an opportunity to more fully explore the relative importance of the electronic and steric factors that appear to influence regioselectivity, and these studies are planned for future publication.

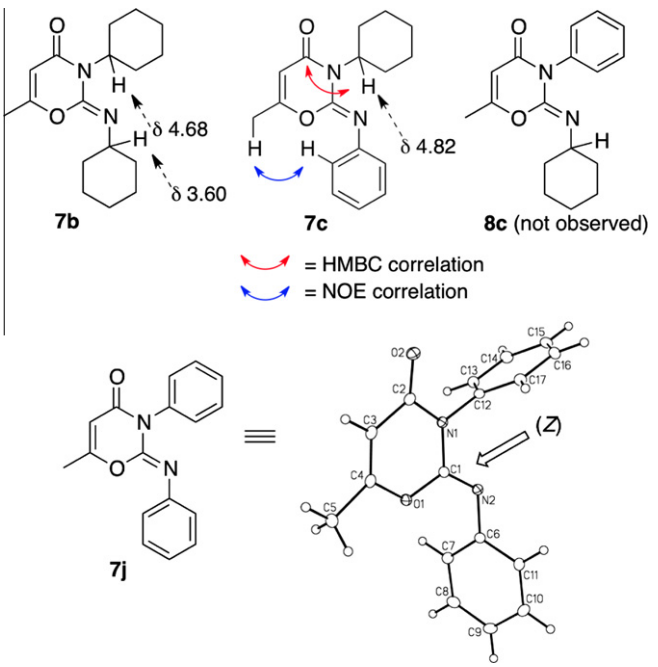
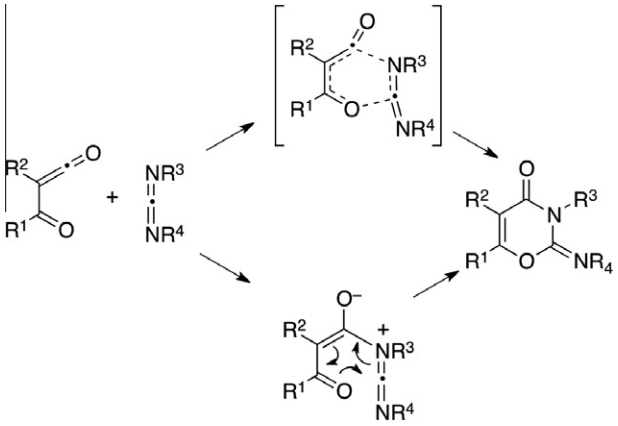


Figure 3. Evidence for regiochemical assignment.



Scheme 3. Mechanism and regioselectivity.

Cycloaddition of thermally generated acylketenes with carbodiimides offers a convergent and expedient route to the iminooxazinone skeleton. Examination of a series of unsymmetrically substituted reaction partners has shown that high levels of regioselectivity can be expected from this process, with the nitrogen atom that is less nucleophilic or more sterically encumbered occupying a position on the exocyclic imino group. Microwave heating allows for clean conversion in relatively short reaction times. Further applications of this work, including the examination of other mixed carbodiimides and the exploration of alternative acylketene precursors, will be described in due course.

Acknowledgements

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References and notes

1. (a) March, L. C.; Romanchick, W. A.; Bajwa, G. S.; Joulié, M. M. *J. Med. Chem.* **1973**, *16*, 337–342; (b) Bereznak, J. F.; Marshall, PCT Int. Appl. (2000), WO 2000051992 A1 20000908.
2. (a) Lacey, R. N. *J. Chem. Soc.* **1954**, 845–849; (b) Lacey, R. N.; Ward, W. R. *J. Chem. Soc.* **1958**, 2134–2141.
3. Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1986**, *69*, 1585–1587.
4. May, E. L. *J. Med. Chem.* **1967**, *10*, 505–506.
5. Capuano, L.; Kirn, H. R.; Zander, R. *Chem. Ber.* **1976**, *109*, 2456–2461.
6. Lisovenko, N. Y.; Maslivets, A. N.; Aliev, Z. G. *Russ. J. Org. Chem.* **2007**, *43*, 117–120.
7. Sato, M.; Ogasawara, H.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 2602–2608.
8. (a) Kappe, C. O.; Färber, G.; Wentrup, C.; Kollenz, G. *J. Org. Chem.* **1992**, *57*, 7078–7083; (b) Saidi, K.; Shaterian, H.; Aghaei, D. *Heterocycl. Commun.* **2000**, *6*, 93–96.
9. Shelkov, R.; Nahmany, M.; Melman, A. *J. Org. Chem.* **2002**, *67*, 8975–8992.
10. Gudipati, I. R.; Sadasivam, D. V.; Birney, D. M. *Green Chem.* **2008**, *10*, 275–277.
11. (a) Palomo, C.; Mestres, R. *Synthesis* **1981**, 373–374; (b) Schlama, T.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1996**, *37*, 7047–7048; (c) Babcock, J. R.; Sita, L. R. *J. Am. Chem. Soc.* **1998**, *120*, 5585–5586; (d) Anderson, J. C.; Bou-Moreno, R. *Tetrahedron* **2010**, *66*, 9182–9186; (e) Kong, K. H.; Tan, C. K.; Lin, X.; Lam, Y. *Chem. Eur. J.* **2012**, *18*, 1476–1486; (f) Kim, S.; Yi, K. Y. *Tetrahedron Lett.* **1985**, *26*, 1661–1664; (g) Olimpieri, F.; Volonterio, A.; Bellucci, M. C.; Zanda, M. *Eur. J. Org. Chem.* **2009**, 6179–6188.
12. Cramer, N.; Buchweitz, M.; Laschat, S.; Frey, W.; Baro, A.; Mathieu, D.; Richter, C.; Schwalbe, H. *Chem. Eur. J.* **2006**, *12*, 2488–2503.
13. Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 6847–6850.

14. Note that commercially available **5a** contains 5% acetone. The role of acetone in promoting the effectiveness of microwave heating is unclear, since the solvent (DCE) has a significantly higher loss factor (tanδ) than acetone. See Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284.
15. Compound **7j** was obtained unexpectedly from the attempted reaction of **5a** with crude 3-benzyl-1-phenylcarbodiimide. We postulate that this product, formed in low yield, arose from preferential reaction with traces of the more reactive diphenylcarbodiimide, which appears to have been formed inadvertently during the preparation of the mixed 3-benzyl-1-phenylcarbodiimide.
16. Larksarp, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 6229–6233.