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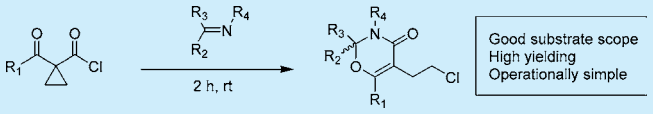
Expedient Metal-Free Synthesis of 1,3-Oxazinen-4-ones

Alexander J. Craig, Louise van der Salm, Lars Stevens-Cullinane, Nigel T. Lucas, Eng Wui Tan, and Bill C. Hawkins*

Department of Chemistry, University of Otago, Dunedin 9054, New Zealand

Supporting Information

ABSTRACT: 1,3-Oxazinen-4-ones are medicinally important scaffolds which have traditionally been accessed using a hetero-Diels–Alder approach or more recently using a cobalt-catalyzed three-component cycloaddition. Herein we report a novel strategy to access this scaffold which allows for the rapid and high yielding synthesis of 1,3-oxazinen-4-ones under ambient temperature and pressures with improved substrate scope.

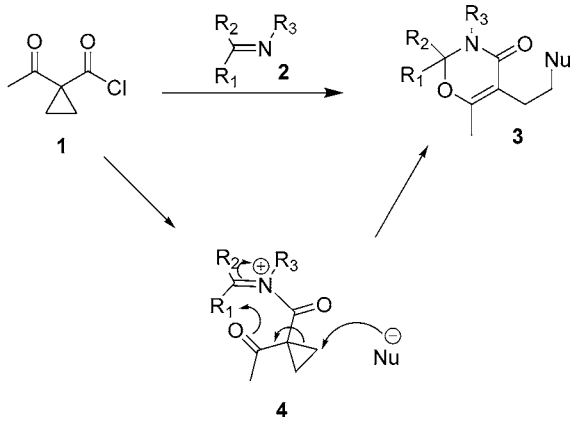


Numerous oxazine- and oxazinone-containing compounds have been shown to possess biological activity against a variety of targets including cancer[1,2] and microbial infections.[3] The clinically used benzodiazepine ketazolam contains an oxazinone and is prescribed for the treatment of anxiety.[4] In addition, this scaffold has proven useful in the design of conformationally restricted peptides and mimics.[5] Access to this structure type has traditionally been achieved using either a hetero-Diels–Alder approach[6−8] or a condensation-type reaction between a hydroxyl amide and a carbonyl-containing fragment.[9−12] These procedures are not ideal, as the preparation of the intermediates is often long and the cyclization itself is typically low yielding, with limited substrate scope predominantly due to the requirement for harsh reaction conditions. Palladium-catalyzed carbonylation of α-diazocarbonyl compounds with imines has also been used to access a small subset of oxazinenones.[13] Most recently, two groups independently reported the synthesis of various 1,3-oxazinan-4-ones using a cobalt-catalyzed three-component cycloaddition.[14,15] While an elegant solution to access these compounds, the reaction does suffer from limitations, namely the requirement of a catalyst, high pressures of carbon monoxide (800–880 psi), and long reaction times of up to 96 h at elevated temperatures (between 50 and 70 °C). Furthermore, no electron-deficient aryloxazinanones were described, and only a limited subset of alkyloxazinanones was reported.

Nucleophilic ring opening of doubly activated cyclopropanes has been known for over a century.[16] Pioneering work by Danishefsky[17−20] and others[21−23] has led to a greater understanding of their reactivity. Traditionally, there has been an emphasis on intramolecular reactions;[24−26] however, reports on the more difficult intermolecular ring-opening of cyclopropyl adducts have become more frequent, albeit with an emphasis on donor–acceptor cyclopropanes.[27−30] Intermolecular nucleophilic ring-opening of cyclopropanes typically requires elevated reaction temperatures, high pressure, or organometallic catalysts.[31−38] Under these conditions other processes often compete, for example, intramolecular rearrangement of the cyclopropane.[26,39]

We sought to investigate the nucleophilic ring opening of the doubly activated *N*-acyliminium cyclopropane **4** (Scheme 1) and

Scheme 1. Synthetic Strategy To Access Oxazinenones



postulated that this electrophilic cyclopropane could undergo a homologous Michael addition with an appropriate nucleophile. The resultant enolate would then attack the iminium carbon to form the corresponding oxazinenone **3**.

Herein we report a general method to access highly functionalized 1,3-oxazinen-4-ones under atmospheric pressure and ambient temperatures with excellent atom economy and without the requirement of additional reagents.

To test our hypothesis, in the first instance the acid chloride **1** was generated in situ prior to the addition of 2 equiv of the diphenyliminoglycinate **6a** (Scheme 2). After 30 min at room temperature, the chloroethyl-1,3-oxazinen-4-one **7a** was isolated as the sole product in a 35% yield. Evidence for the structure of **7a** was provided by analysis of the proton NMR spectrum which showed the disappearance of resonances attributed to the cyclopropane at 1.95 and 1.73 ppm and the presence of two 2H triplets at 3.32 and 2.64 ppm, consistent with ring-opening of the

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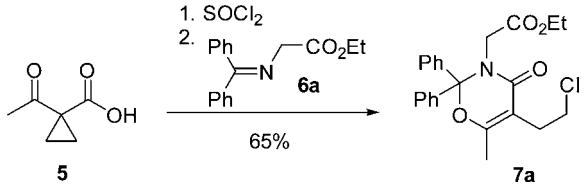
Scheme 2. Synthesis of Oxazinenone 7a



cyclopropane. Analysis of the mass spectrum indicated a sodiated molecular ion (m/z 436.1292 Da) with an isotopic pattern consistent with a chlorine atom being present in the structure. Furthermore, the carbon NMR spectrum of **7a** was devoid of any resonance attributable to an isolated ketone along with the emergence of a resonance at 96.7 ppm which was assigned to a diheteroatom substituted quaternary carbon, in line with oxazinenone formation. Confirmation of the structure of **7a** was provided by a single-crystal X-ray diffraction study (Figure 1).

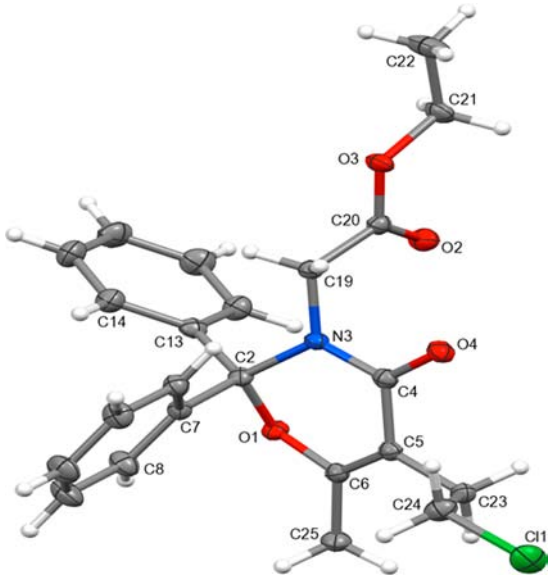
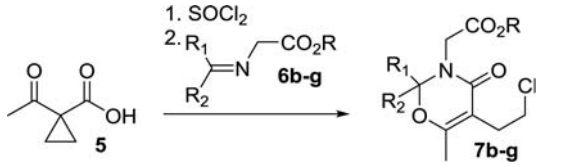


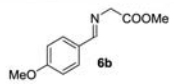
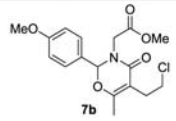
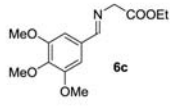
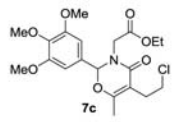
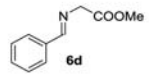
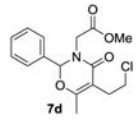
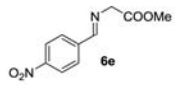
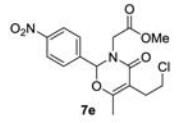
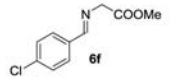
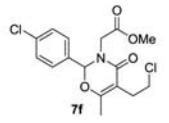
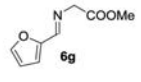
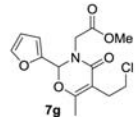
Figure 1. X-ray single-crystal molecular structure of **7a**.

The structure of **7a** is somewhat surprising as the imine was expected to out-compete the less nucleophilic chloride which, at least initially, would be in considerably lower concentrations than the imine. An improvement in the overall yield for this reaction was achieved by not isolating the crude acid chloride; dilution of the reaction mixture with DCM followed by the addition of 2 mol equiv of the imine provided the corresponding oxazinenone **7a** in a 65% yield over 2 steps (Scheme 2).[40] Notably, increasing the relative amount of imine beyond 2 mol equiv did not alter the product or chemical yield of the oxazinenone.

With the view toward creating greater molecular diversity and probing the electronic requirements for oxazinenone formation, the iminoglycinates (**6b–g**, Table 1) were synthesized using standard procedures.[40] Electronically diverse 4-substituted arylimines were well-tolerated with good yields of the corresponding oxazinenones observed for electron rich (entry 1) including (3,4,5-trimethoxybenzyl)iminoglycinate (entry 2), relatively neutral (entry 3), and electron-poor (entry 4) imines. The tolerance for electron-poor aromatic systems has not been reported for the cobalt-catalyzed cycloadditions.[14,15] Furthermore, the readily functionalized aryl halide and heteroaromatic examples (entries 5 and 6) also proceed in good yield, 52% and 58%, respectively. Treatment of the cyclopropyl acid chloride **1** with benzylamine cleanly provided the corresponding cyclopropyl benzylamide with no evidence of ring-opened adducts found (not shown).

Table 1. Iminoglycinate Substrate Scope for Oxazinenone Synthesis



entry No.	imine	product[a]	yield[b]
1			52
2			61
3			81
4			63
5			52
6			58

[a]Reaction conditions: cyclopropyl carboxylic acid **5** (1.0 equiv), thionyl chloride (1.1 equiv), 90 min, 40 °C, then DCM and imine (2 equiv), rt, 2 h. [b]Isolated yield over two steps.

Driven by this success and the possibility of providing a robust route to oxazinenones, we examined the benzyl benzylidene system **8a–l** (Figure 2).[40] Under the standard reaction conditions described above, access to the corresponding oxazinenones was achieved in less than 2 h at room temperature and in moderate to good yields. As observed for the iminoglycinate analogues, diversity in aromatic substitution patterns and electronics was well tolerated. The sterically demanding but electron-rich *o*-methoxy-substituted aromatic imine underwent reaction with the acid chloride **1** to provide the corresponding oxazinenone **9b** in 52% yield. Furthermore, both electron-rich and electron-poor *meta*-substituted aryl imines underwent smooth conversion to their corresponding oxazine-

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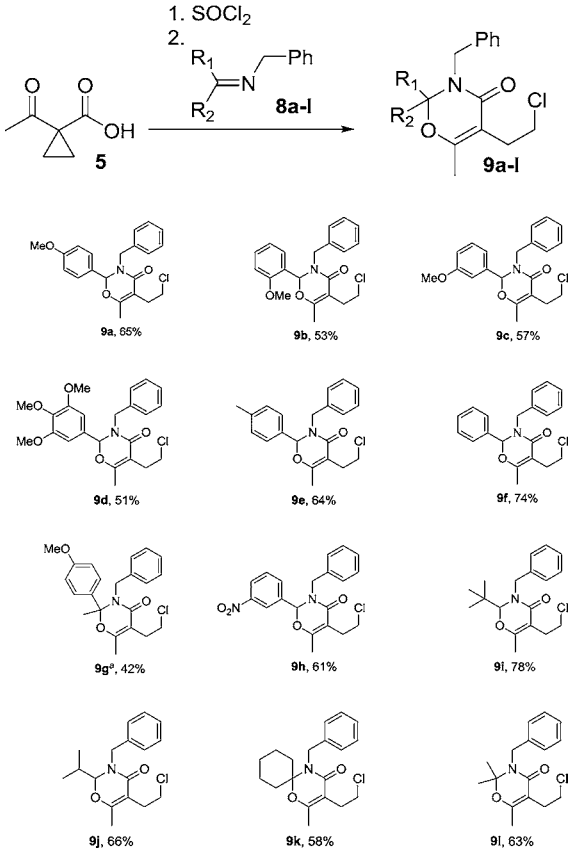


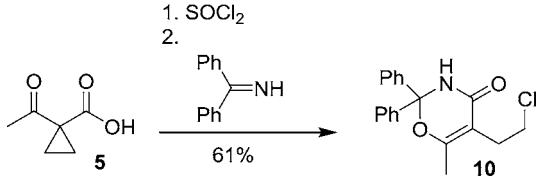
Figure 2. Imine substrate scope for oxazinenone synthesis. Reaction conditions: cyclopropyl carboxylic acid **5** (1.0 equiv), thionyl chloride (1.1 equiv) 90 min, 40 °C, then DCM and imine (2 equiv), rt, 2 h. (a) Coeluted with trace amounts of an unknown byproduct.

nones **9c** and **9h**, respectively. Alkylimines were also well tolerated with *tert*-butyl **9i**, isopropyl **9j**, cyclohexyl **9k**, and dimethyl **9l** oxazinenones all being isolated in good yield under the standard reaction conditions. Analysis of the reaction mixtures by proton NMR prior to purification by silica gel chromatography indicated complete conversion to the corresponding oxazinenone with only trace impurities present.[40] Mass recovery was typically greater than 90% prior to chromatography with an appreciable loss of product generally observed during purification.

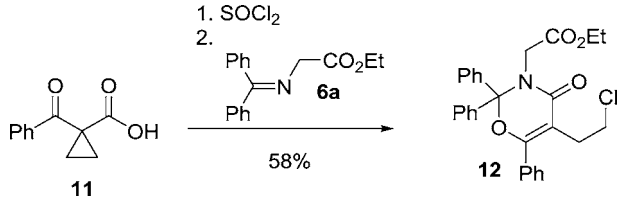
Further reaction scope in the imine portion was demonstrated by treatment of the acid chloride **1** with benzophenone imine to provide the readily functionalized secondary amide **10** in 61% yield (Scheme 3).

Having established good substrate scope on the imino portion of the oxazinenone, we turned our attention to modifying the cyclopropyl acid fragment. The known benzoylcyclopropane **11**[41] was treated with thionyl chloride to provide the corresponding cyclopropyl acid chloride, which readily participated in the reaction with diphenyliminoglycinate to afford the triphenyl oxazinenone **12** in 58% yield (Scheme 4).

Scheme 3. Synthesis of Oxazinenone 10

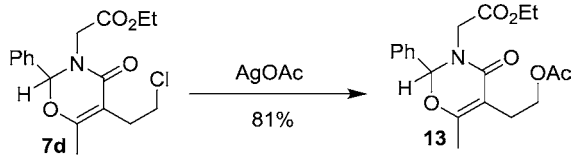


Scheme 4. Synthesis of Oxazinenone 12



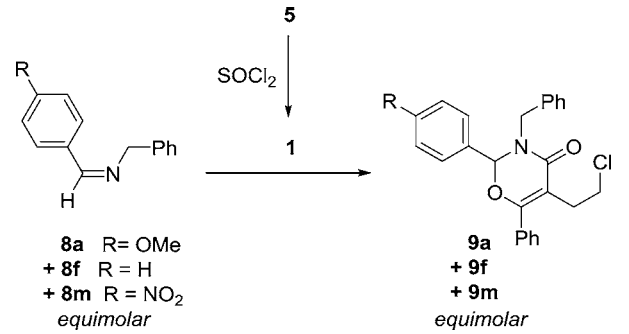
Efforts to vary the acid chloride itself by generating a mixed anhydride or employing other activated acids were unsuccessful in producing the corresponding oxazinenones. Instead, functionalization of the alkyl side chain was achieved by treatment of the oxazinenone **7d** with silver acetate to afford the corresponding acetate **13** in an 81% yield (Scheme 5).

Scheme 5. Modification of the Alkyl Halide Side Chain of Oxazinenone 7d



The versatility of this reaction was further demonstrated by a competition experiment whereby equimolar amounts of 4-methoxybenzyl-, benzyl-, and 4-nitrobenzylimines were added to 1 molar equiv of the acid chloride **1** under the standard reaction conditions (Scheme 6). Analysis of the proton NMR spectrum of

Scheme 6. Competition Experiment with Electronically Diverse Imines Afforded an Equimolar Mixture of Corresponding Oxazinenones 9a,f,m



the crude mixture indicated an equimolar mixture of the corresponding oxazinenones. This is in agreement with the substrate flexibility and uniform yields of electron-rich through to electron-poor aryl imines demonstrated in Table 1 and Figure 2.

In conclusion, we have described a robust new method to gain access to a diverse range of oxazinenones under mild reaction conditions without the requirement of a metal catalyst or pressure. The cyclopropyl carboxylic acid and imine precursors are readily prepared with a range of substituents and functional groups. Efforts to further investigate the mechanism of this reaction are underway and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds and X-ray crystallographic data for **7a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bhawkins@chemistry.otago.ac.nz.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Sam Zard (Ecole Polytechnique) with respect and admiration.

■ REFERENCES

(1) Moreno, L.; Cabedo, N.; Boulange, A.; Parraga, J.; Galan, A.; Leleu, S.; Sanz, M.-J.; Cortes, D.; Franck, X. *Eur. J. Med. Chem.* **2013**, *69*, 69−76.

(2) Basappa; Murugan, S.; Kavitha, C. V.; Purushothaman, A.; Nevin, K. G.; Sugahara, K.; Rangappa, K. S. *Cancer Lett.* **2010**, *297*, 231−243.

(3) Hossan, A. S. M.; Abu-Melha, H. M. A.; Al-Omar, M. A.; Amr, A. E.-G. E. *Molecules* **2012**, *17*, 13642−13655.

(4) Basmajian, J. V.; Shankardass, K.; Russell, D.; Yucel, V. *Arch. Phys. Med. Rehabil.* **1984**, *65*, 698−701.

(5) Loughlin, W. A.; Tyndall, J. D. A.; Glenn, M. P.; Hill, T. A.; Fairlie, D. P. *Chem. Rev.* **2010**, *110*, PR32−PR69.

(6) Sato, M.; Ogasawara, H.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 2602−2608.

(7) Watanabe, Y.; Washio, T.; Krishnamurthi, J.; Anada, M.; Hashimoto, S. *Chem. Commun.* **2012**, *48*, 6969−6971.

(8) Panunzio, M.; Tamanini, E.; Bandini, E.; Campana, E.; D'Aurizio, A.; Vicennati, P. *Tetrahedron* **2006**, *62*, 12270−12280.

(9) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wagatsuma, N.; Kohagisawa, T.; Inoue, H. *Heterocycles* **1978**, *9*, 819−830.

(10) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181−4183.

(11) Schmidt, J. P.; Beltrán-Rodil, S.; Cox, R. J.; McAllister, G. D.; Reid, M.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 4041−4044.

(12) Cayley, A. N.; Gallagher, K. A.; Ménard-Moyon, C.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Synthesis* **2008**, 3846−3856.

(13) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330−4341.

(14) Liu, L.; Sun, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9865−9869.

(15) Zhang, Y.; Ji, J.; Zhang, X.; Lin, S.; Pan, Q.; Jia, L. *Org. Lett.* **2014**, *16*, 2130−2133.

(16) Best, S. R.; Thorpe, J. F. *J. Chem. Soc.* **1909**, *95*, 685−714.

(17) Danishefsky, S.; Rovnyak, G. *J. Chem. Soc., Chem. Commun.* **1972**, 820−821.

(18) Danishefsky, S.; Rovnyak, G. *J. Chem. Soc., Chem. Commun.* **1972**, 821−822.

(19) Danishefsky, S.; Singh, R. K. *J. Am. Chem. Soc.* **1975**, *97*, 3239−3241.

(20) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66−72.

(21) Stork, G.; Marx, M. *J. Am. Chem. Soc.* **1969**, *91*, 2371−2373.

(22) Trost, B. M.; Frazee, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 6124−6126.

(23) Pellacani, L.; Tardella, P. A.; Loreto, M. A. *J. Org. Chem.* **1976**, *41*, 1282−1283.

(24) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778−4782.

(25) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573−576.

(26) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804−818.

(27) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122−3123.

(28) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688−9692.

(29) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051−3060.

(30) Zhou, Y.-Y.; Wang, L.-J.; Li, J.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9066−9069.

(31) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949−5952.

(32) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023−3026.

(33) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809−2812.

(34) Sapeta, K.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 2081−2084.

(35) Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 4180−4183.

(36) Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem.* **2012**, *77*, 6634−6637.

(37) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558−2561.

(38) Martin, M. C.; Patil, D. V.; France, S. *J. Org. Chem.* **2014**, *79*, 3030−3039.

(39) Mack, D. J.; Njardarson, J. T. *ACS Catal.* **2013**, *3*, 272−286.

(40) For further details, see the Supporting Information.

(41) Jahngen, E. G. E.; Phillips, D.; Kobelski, R. J.; Demko, D. M. *J. Org. Chem.* **1983**, *48*, 2472−2476.