ARTICLE IN PRESS

Tetrahedron Letters xxx (2014) xxx-xxx

Contents lists available at ScienceDirect





journal homepage: www.elsevier.com/locate/tetlet



Efficient access to 3-substituted- γ -hydroxylactams: the uncatalyzed addition of diorganozinc reagents to cyclic imides with heterocyclic substitution

Kimberly S. DeGlopper, Joseph M. Dennis, Jeffrey B. Johnson*

Department of Chemistry, Hope College, 35 East 12th St, Holland, MI 49423, USA

ARTICLE INFO

Article history: Received 17 January 2014 Revised 23 January 2014 Accepted 28 January 2014 Available online xxxx

Keywords: Imides Organozinc reagents Nucleophilic addition Directing groups

ABSTRACT

A range of 3-substituted- γ -hydroxylactams have been prepared via the uncatalyzed addition of organozinc nucleophiles to cyclic imides. This reactivity is primarily limited to imides containing heterocyclic *N*substitution, but proceeds efficiently with a variety of diorganozinc reagents, including those prepared and utilized without purification, as well as organozinc halides. It is hypothesized that the presence of a Lewis basic directing group is required for optimum reactivity.

© 2014 Elsevier Ltd. All rights reserved.

Introduction

The use of Lewis basic functionality to direct reactivity has long been utilized to control the formation of complex organic species.¹ Recent studies have repeatedly demonstrated the significance of these groups on transition metal catalysis,² particularly within the realm of inert bond activation, such as that occurring with C-H³ and C–C bonds.⁴ The presence of a directing group can be utilized to control stereochemistry, enhance regioselectivity, or even promote reactions that fail to proceed in the absence of such a group. In the course of exploring the substrate scope for our recently reported methodology utilizing nickel species to catalyze the addition of diorganozinc reagents to phthalimides,⁵ we observed that substrates containing heteroaromatic directing groups within phthalimide nitrogen substitution undergo reaction in the absence of nickel. Herein we present our efforts to optimize the substrate-directed, selective mono-addition of diorganozinc nucleophiles to N-substituted imide moieties while examining the scope of amenable substituents that promote the uncatalyzed addition.

The addition of nucleophilic aryl reagents to phthalimides provides ready access to substituted 3-hydroxy-γ-lactams, a structural motif observed in numerous biologically active molecules,^{6,7} including chlorthalidone, a diuretic utilized to treat hypertension.⁸

http://dx.doi.org/10.1016/j.tetlet.2014.01.130 0040-4039/© 2014 Elsevier Ltd. All rights reserved. Access to these hydroxy-lactams can be achieved through traditional nucleophilic addition utilizing Grignard or lithium reagents, but these reactions are often fraught with uncontrolled multiple additions that lead to complex product mixtures.⁹ Several more recently developed methods, including rhodium-catalyzed oxidative acylation¹⁰ and the utilization of alkynyl benzoic acids,¹¹ work well for simple structures but generally fail to demonstrate broad substrate scope, notably for inclusion of heteroatoms within the nitrogen substituent.¹²

Results and discussion

In a recent publication, we reported the use of nickel catalysis to achieve the selective mono-addition of diorganozinc reagents to



Scheme 1. Uncatalyzed addition of diorganozinc reagents to imides containing heterocyclic substitution.

^{*} Corresponding author. Tel.: +1 616 395 7083; fax: +1 616 395 7118. *E-mail address: jjohnson@hope.edu* (J.B. Johnson).

K. S. DeGlopper et al./Tetrahedron Letters xxx (2014) xxx-xxx

2

Table 1

Scope of imide substituents for the uncatalyzed direct addition of diethylzinc^a



Entry	R	Product	Yield (%)
1	2-Pyridyl	2	83
2	6-Methyl-2-pyridyl	3	78
3	3-Pyridyl	4	82
4	4-Pyridyl	5	<5
5	2-Thiazolyl	6	71
6	$N(CH_3)_2$	7	35
7	OCH ₂	8	<5

 a Standard conditions: Imide (0.5 mmol), Et_2Zn (0.55 mmol), THF (2 mL), 55 °C, argon or nitrogen atmosphere.



Scheme 2. A sample of substrates that fail to undergo direct addition.

phthalimides. In the course of performing control experiments, it was observed that while the vast majority of *N*-substituted phthalimides require a nickel catalyst to react with diorganozinc reagents, *N*-(2-pyridyl)-phthalimide (**1**) undergoes alkylation in the absence of a transition metal catalyst (Scheme 1). At 55 °C in THF under an inert atmosphere over 16 h, diethylzinc is added to **1** to generate hydroxy-lactam **2** in 83% yield following workup and purification.¹³

To examine the influence of the heteroaromatic substituent, a series of additional imides were prepared and subjected to similar reaction conditions. Substrates containing 2- and 3-pyridines and 2-thiazolyl react smoothly, each producing the desired hydroxy-lactam in good to excellent yields (Table 1). To our surprise, the 4-pyridyl phthalimide failed to undergo reaction, yielding unreacted starting materials even after extended reaction times, leading to the conclusion that the observed reactivity is due, at least in part, to the relative proximity of heteroatoms on the *N*-substituent and the coordination of the diorganozinc reagents during the course of the reaction.

Table 3

Use of 3,4-dimethylmaleimide backbone^a



Entry	R	Source	Product	Yield (%)
1	Et	Et ₂ Zn	17	84
2	Ph	Ph ₂ Zn	18	91
3	3,5-(CF ₃) ₂ -C ₆ H ₃	Ar ₂ Zn ^b	19	74
4	4-OMe-C ₆ H ₄	Ar ₂ Zn ^b	20	95
5	4-OMe-C ₆ H ₄	ArZnCl ^c	20	81

^a Standard conditions: Imide (0.5 mmol), nucleophile (0.55 mmol), THF (2 mL),
 55 °C under an argon or nitrogen atmosphere.
 ^b Diorganozinc reagent generated from aryl bromide, *n*BuLi, and ZnCl₂ and used

^D Diorganozinc reagent generated from aryl bromide, nBuLi, and ZnCl₂ and used without purification.

 $^{\rm c}$ Organozinc halide generated from aryl bromide, $n{\rm BuLi},$ and ${\rm ZnCl}_2$ and used without purification.

Beyond coordination effects, electronics may play a role, as the heteroaromatic substrates are all significantly electron deficient. To probe this possibility, a series of phthalimides with electron deficient *N*-aryl substituents were prepared and tested under the standard reaction conditions. None of these substrates, which included 3,5-bis(trifluoromethyl)-, pentafluoro-, and 4-nitro-phenyl moieties, reacted with diethylzinc. These results suggest that the coordination event is required for the uncatalyzed reaction.

Beyond heteroaromatic substituents, *N*-(dimethylamino) phthalimide also undergoes reaction with diethylzinc, albeit in only 35% yield (Table 1, entry 6). Notably, the analogous *N*-methoxy phthalimide (Table 1, entry 7) does not show similar behavior, even at extended reaction times. Similarly, amine-substituted phthalimide **9** and *N*-(2-methoxyphenyl)phthalimide (Scheme 2), each of which contains potential directing functionality, also fails to react under the standard conditions.

With the scope of amenable heteroatom substituents in hand, several other nucleophiles were examined for reactivity, using *N*-(2-pyridyl)phthalimide (**10**) and *N*-2-thiazolyl-phthalimide (**11**) as the test substrates. The reaction proceeds remarkably efficiently using commercially available diphenylzinc, producing desired hydroxy-lactams **12** and **13** in 95% and 94% yield, respectively (Table 2). As with our previous work, the reaction also proceeds efficiently with diorganozinc reagents generated from the corresponding aryl bromide via lithium–halogen exchange and reaction

Table 2

Scope of nucleophiles amenable to direct addition to heterocycle-substituted imides^a



Entry	Substrate	R	Nucleophile/source	Product	Yield (%)
1	10 (Ar = 2-pyridyl)	Ph	Ph ₂ Zn, commercial	12	95
2	11 (Ar = 2-thioazolyl)	Ph	Ph ₂ Zn, commercial	13	94
3	10	$4-OCH_3C_6H_4$	Ar ₂ Zn, from ArBr, BuLi, ZnCl ₂	14	90
4	10	$4-OCH_3C_6H_4$	ArZnCl, from ArBr, BuLi, ZnCl ₂	14	72
5	10	3,5-(CF ₃) ₂ C ₆ H ₃	Ar ₂ Zn, from ArBr, BuLi, ZnCl ₂	15	77
6	10	3,5-(CF ₃) ₂ C ₆ H ₃	ArZnCl, from ArBr, BuLi, ZnCl ₂	15	56
7	10	Ph	PhB(OH) ₂ , commercial	12	>5

^a Standard conditions: Imide (0.5 mmol), nucleophile (0.55 mmol), THF (2 mL), 55 °C, argon or nitrogen atmosphere.

Please cite this article in press as: DeGlopper, K. S.; et al. Tetrahedron Lett. (2014), http://dx.doi.org/10.1016/j.tetlet.2014.01.130



Scheme 3. Product mixture obtained from imides with saturated backbones.

with ZnCl₂ as demonstrated with both electron rich and electronic deficient species (Table 2, entries 3 and 5). Notably, these nucleophiles can be prepared and utilized without purification with no significant effect upon the reaction yield. In a similar fashion, organozinc halides also efficiently produce the desired hydroxy-lactam products, albeit in slightly reduced yield (entries 4 and 6). Notably, boronic acids fail to react under the standard reaction conditions (entry 7).

In contrast to our recent nickel-catalyzed coupling of phthalimides and diorganozinc reagents,^{5,14} this reaction also proceeds with other cyclic imides. While the use of maleimides was complicated by competing conjugate addition, the use of *N*-(2-pyridyl)-3,4-dimethyl maleimide (**16**)¹⁵ led to the desired products with a range of nucleophiles, including diorganozinc and organozinc halides (Table 3), in very good yields. The use of imides with saturated backbones, however, such as imide **21** in Scheme 3, generates a mixture of alkene products, presumably formed via desired diorganozinc addition followed by elimination.

In summary, we have observed the substrate-specific uncatalyzed addition of diorganozinc reagents to cyclic imides. Nucleophilic addition occurs very efficiently with heteroaromatic-containing substrates, presumably via the coordination of the diorganozinc reagent. This work uncovers the importance of directing groups in simple reactivity, and presents an efficient and selective production of 3-substituted- γ -hydroxylactams containing appended heterocyclic moieties.

Acknowledgments

Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund (50347-UNI1), the Towsley Foundation, and the NSF (CHE-1148719) for financial support of this research. Grants from the NSF for the purchase of NMR spectrometers (CHE-0922623) and GC/MS instrumentation (CHE-0952768) are also gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01. 130. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

- 1. For leading references, see: Denmark, S. E.; Beutner, G. L. Angew. Chem., Int. Ed. 2008, 47, 1560.
- 2. Rousseau, G.; Breit, B. Angew. Chem., Int. Ed. 2011, 50, 2450.
- For leading references, see: (a) Neufeldt, S. R.; Sanford, M. S. Acc. Chem Res. 2012, 45, 936; (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Acc. Chem. Res. 2012, 45, 814; (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Acc. Chem. Res. 2012, 45, 788; (d) Daugulis, O.; Do, H.-Q.; Shabashov, D. Acc. Chem. Res. 2009, 42, 1074.
- For examples, see: (a) Dreis, A. M.; Douglas, C. J. J. Am. Chem. Soc. 2009, 131, 412; (b) Park, Y. J.; Park, J.-W.; Jun, C.-H. Acc. Chem. Res. 2008, 41, 222; (c) Bart, S. C.; Chirik, P. J. J. Am. Chem. Soc. 2003, 125, 886.
- Dennis, J. M.; Calyore, C. M.; Sjoholm, J. S.; Lutz, J. P.; Gair, J. J.; Johnson, J. B. Synlett 2013, 2567.
- Mikolasch, A.; Hessel, S.; Salazar, M. G.; Neumann, H.; Manda, K.; Gördes, D.; Schmidt, E.; Thurow, K.; Hammer, E.; Lindequist, U.; Beller, M.; Schauer, F. Chem. Pharm. Bull. 2008, 56, 781.
- (a) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, 30, 2747; (b) Fajardo, B.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett.* **1982**, 23, 39; (c) Abu Zarga, M. H.; Sabri, S. S.; Firdous, S.; Shamma, M. *Phytochemistry* **1987**, 26, 1233.
- Topliss, J. G.; Konzelman, L. M.; Sperber, N.; Roth, F. E. J. Med. Chem. 1964, 7, 453.
- For successful examples, see: (a) Wang, E.-C.; Chen, H.-F.; Feng, P.-K.; Lin, Y.-L.; Hsu, M.-K. *Tetrahedron Lett.* **2002**, 43, 9163; (b) Bousquet, T.; Fleury, J.-F.; Daïch, A.; Netchaitaïlo, P. *Tetrahedron* **2006**, 62, 706; (c) Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1996**, 37, 7707.
- 10. Sharma, S.; Park, E.; Park, J.; Kim, I. S. Org. Lett. 2012, 14, 906.
- Zhou, Y.; Zhai, Y.; Li, J.; Ye, D.; Jiang, H.; Liu, H. Green Chem. 2010, 12, 1397.
 A photodecarboxylative process: (a) Griesbeck, A. G.; Oelgemöller, M. Synlett
- A photodecarboxylative process: (a) Griesbeck, A. G.; Oelgemöller, M. Synlett 1999, 492. Difluroalkyl nucleophiles; (b) Bootwicha, T.; Panichakul, D.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. J. Org. Chem. 2009, 74, 3798.
- 13. See the Supplementary material for all experimental details.
- Havlik, S. E.; Simmons, J. M.; Winton, V. J.; Johnson, J. B. J. Org. Chem. 2011, 76, 3588.
- Baumann, M. E.; Bosshard, H.; Breitenstein, W.; Rihs, G.; Winkler, T. *Helv. Chim. Acta* **1984**, 67, 1897.