ORGANIC LETTERS

2001
Vol. 3, No. 14
2173−2176

Solid-Phase Rhodium Carbenoid Reactions: An N–H Insertion Route to a Diverse Series of Oxazoles

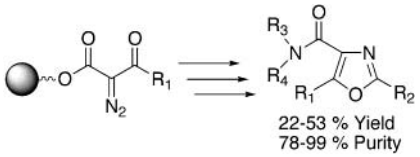
Bruce Clapham, Carsten Spanka,[†] and Kim D. Janda*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

kdjanda@scripps.edu

Received April 18, 2001

ABSTRACT



The solid-phase synthesis of a series of oxazoles is described. The key step in the construction of these molecules involves the rhodium-catalyzed decomposition of polymer-bound α-diazo-β-ketoesters. These reactions are performed in the presence of primary amides and yield the corresponding N–H insertion products. Subsequent cyclodehydration of these α-(acylamino)-β-ketoesters provides the corresponding resin-bound 2,5-disubstituted oxazoles, which are further elaborated during cleavage from the resin.

The past decade has seen extensive research in the preparation of a wide variety of combinatorial libraries. These libraries may be screened to obtain "hits" of potential value in pharmaceutical, agricultural, or material science applications.[1] A large portion of this research has involved the use of solid-phase organic synthesis (SPOS). Originally developed for the synthesis of peptides,[2] SPOS has been used in the preparation of a plethora of small-molecule libraries and complex natural products.[3] However, adaption of conventional solution-phase chemistry to the solid phase is not always straightforward. Consequently, great efforts have been made to optimize many of the reactions available from the organic chemist's arsenal for use with solid-phase methodology.[4]

One important class of transformations in organic synthesis are those involving substrates that contain the diazo functionality.[5] Diazo compounds decompose when treated with either Lewis acid or transition metal catalysts and form highly reactive carbene or carbenoid species. These intermediates react via a number of mechanisms including insertion into C−H or heteroatom (X−H) bonds to form new intra- or intermolecular bonds. Although diazocarbon chemistry constitutes an important class of reactions, solid-phase applications have been limited to a few exceptional examples.[6]

α-Diazoketones, α-diazoacetates, and α-diazo-β-ketoesters are useful substrates for the construction of heterocyclic compounds including oxazoles.[7] However, most naturally occurring oxazoles are formed by posttranslational modification of serine and threonine residues in peptides.[8] Numerous oxazole-containing natural products have been isolated, and

[†] Novartis Pharma AG, CH-4002, Basel, Switzerland.

(1) Bunin, B. A. *The Combinatorial Index*; Academic Press Ltd.: London, 1998.

(2) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

(3) (a) *Solid-Phase Organic Synthesis*; Czarnik, A. W., Ed.; John Wiley & Sons Ltd.: New York, 2001. (b) *Solid-Phase Organic Synthesis*; Burgess, K., Ed.; John Wiley & Sons Ltd.: New York, 2000.

(4) (a) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527.

(5) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons Ltd.: New York, 1997.

(6) (a) Nagashima, T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2001**, *123*, 2695. (b) Iso, Y.; Shindo, H.; Hamana, H. *Tetrahedron* **2000**, *56*, 5353. (c) Cano, M.; Camps, F.; Joglar, J. *Tetrahedron Lett.* **1998**, *39*, 9819. (d) Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Austin, D. J. *Tetrahedron Lett.* **1997**, *38*, 7139. (e) Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973. (f) Zaragoza, F.; Petersen, S. V. *Tetrahedron* **1996**, *52*, 5999.

(7) (a) Huisgen, R.; König, H.; Binsch, G.; Sturm, H. J. *Angew. Chem.* **1961**, *73*, 368. (b) Moody, C. J.; Doyle, K. J. *Prog. Heterocycl. Chem.* **1997**, *9*, 1.

10.1021/ol010075n CCC: $20.00
Published on Web 06/20/2001

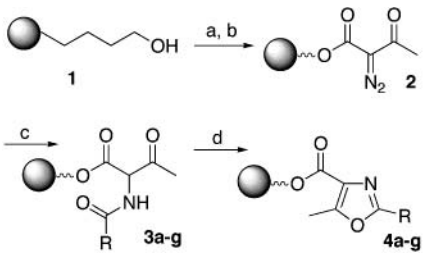
some of these compounds have exhibited interesting biological properties. Hence, many total syntheses and new developments in oxazole methodology have appeared in the recent literature.[9]

Despite the current renaissance in oxazole chemistry, combinatorial applications of oxazoles have been limited. Research has included the synthesis of oxazole-containing peptido-mimetics[10] and the preparation of oxazole-containing peptide macrocycles that could serve as scaffolds for combinatorial elaboration.[11] A recent report described the synthesis of polymer-bound β-silyl-α-diazoketones.[6b] Three examples were given where these diazoketones were converted into oxazoles using a rhodium-catalyzed 1,3-dipolar cycloaddition reaction with a nitrile. Although this work represents an important example of a solid-phase oxazole synthesis, the 1,3-dipolar cycloaddition route to oxazoles can be problematic. Moody and co-workers reported that some nitriles are poor substrates in such reactions and developed an elegant alternative oxazole synthesis.[12] In their approach, an α-diazo-β-ketoester was reacted with a primary amide in the presence of a rhodium catalyst, giving an N−H insertion product. These α-(acylamino)-β-ketoester products were then converted into oxazoles using a cyclodehydration reaction. This N−H insertion route to oxazoles is tolerant of various functional groups, and diverse primary amide coupling partners are readily available. Thus, this chemistry is an ideal choice for the preparation of oxazole libraries.

Some of our own research has focused upon the synthesis of small-ring organic compounds using soluble and insoluble polymer supports.[13] We recently reported an efficient solid-phase synthesis of 1,3-oxazolidines.[14] This prompted us to investigate a solid-phase synthesis of the aromatic oxazole analogues using the N−H insertion strategy. Reported here are our preliminary findings in this area.

The project began by preparing a polymer-bound acetoacetyl ester by reaction of diketene[15] with hydroxybutyl JandaJel™ resin **1**[16] (Scheme 1).

Scheme 1[a]



[a] (a) Diketene (3 equiv), DMAP (10 mol %), CH_2Cl_2, −78 °C to rt, 16 h; (b) dodecylbenzenesulfonylazide (5 equiv), Et_3N (5 equiv), toluene, 16 h; (c) primary amide (5 equiv), Rh_2Oct_4 (2 mol %), toluene, 60 °C, 2 h; (d) Cl_2PPh_3 (2 equiv), Et_3N (6 equiv), CH_2Cl_2, 16 h.

Reaction progress was monitored by the appearance of two peaks at 1734 and 1710 cm^{-1} in the IR spectra, corresponding to the ester and ketone functionality, respectively. Next, diazotransfer was performed under standard conditions[17] using dodecylbenzenesulfonylazide[18] affording α-diazo-β-ketoester **2**. IR analysis of **2** showed an intense absorption at 2137 cm^{-1} corresponding to the diazo functionality. The ester and ketone absorptions of **2** shifted to 1714 and 1655 cm^{-1} indicating complete conversion to product. The loading of resin **2** was estimated using elemental analysis for nitrogen.[19]

With the preparation of α-diazo-β-ketoester **2** complete, an N−H insertion reaction with benzamide was investigated. Treatment of **2** with benzamide (5 equiv) in the presence of rhodium ocatanoate catalyst (2 mol %) in toluene at 60 °C for 2 h gave N−H insertion product **3a** (R = Ph) in 99% yield on the basis of mass balance. This product displayed IR absorptions at 3425, 1749, 1724, and 1633 cm^{-1} corresponding to the N−H stretch and the ester, ketone, and amide carbonyls, respectively. Additionally, **3a** showed complete disappearance of the characteristic diazo IR absorption at 2137 cm^{-1} indicating complete reaction.

Cyclodehydration of N−H insertion product **3a** to polymer-bound oxazole **4a** was more troublesome to optimize. Wipf's mild cyclodehydration procedure (PPh_3, I_2, Et_3N, CH_2Cl_2)

(8) (a) Jack, R. W.; Jung, G. *Curr. Opin. Chem. Biol.* **2000**, *4*, 310. (b) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249.

(9) (a) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533. (b) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301. (c) Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Reader, M.; Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, *15*, 2415. (e) Smith, A. B.; III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Duan, J. J.-W.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Salvatore, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 10478. (f) Mulder, R. J.; Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1999**, *64*, 4995. (g) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924.

(10) (a) Grabowska, U.; Rizzo, A.; Farnell, K.; Quibell, M. *J. Comb. Chem.* **2000**, *2*, 475. (b) Martin, L. M.; Hu, B.-H. *Tetrahedron Lett.* **1999**, *40*, 7951.

(11) (a) Somogyi, L.; Haberhauer, G.; Rebek, J., Jr. *Tetrahedron* **2001**, *57*, 1699. (b) Haberhauer, G.; Somogyi, L.; Rebek, J., Jr. *Tetrahedron Lett.* **2000**, *41*, 5013.

(12) (a) Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J.; Slawin, A. M. Z. *Synlett* **1996**, 825. (b) Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, *13*, 591.

(13) For recent examples, see: (a) López-Pelegrín, J. A.; Janda, K. D. *Chem. Eur. J.* **2000**, *6*, 1917. (b) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859.

(14) Tremblay, M. R.; Wentworth, P., Jr.; Lee, G. E., Jr.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 698.

(15) Gordeev, M. F.; Patel, D. V.; Wu, J.; Gordon, E. M. *Tetrahedron Lett.* **1996**, *37*, 4643.

(16) JandaJel™ resins are available from Aldrich Chemical Co. The hydroxybutyl JandaJel™ resin used was prepared using a similar procedure to that of Harikrishnan (see Supporting Information): Harikrishnan, L. S.; Hollis Showalter, H. D. *Synlett* **2000**, 1339. For further discussion of the JandaJel™ resins, see: (a) Toy, P. H.; Reger, T. S.; Janda, K. D. *Aldrichimica Acta* **2000**, *33*, 87. (b) Toy, P. H.; Reger, T. S.; Garibay, P.; Garno, J. C.; Malikayil, J. A.; Liu, G.; Janda, K. D. *J. Comb. Chem.* **2001**, *3*, 117. (c) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329. For recent applications, see: (d) Brümmer, O.; Clapham, B.; Janda, K. D. *Tetrahedron Lett.* **2001**, *42*, 2257. (e) Clapham, B.; Cho, C.-W.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 868.

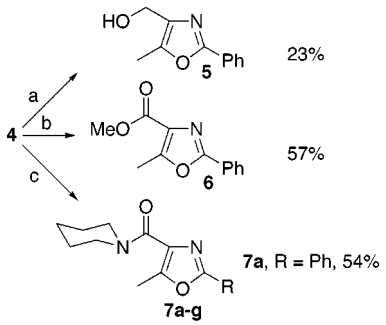
(17) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 179.

(18) Purchased from TCI chemical company. See also: Hazen, G. G.; Bollinger, F. W.; Roberts, F. E.; Russ, W. K.; Seman, J. J.; Staskiewicz, S. *Org. Synth.* **1995**, *73*, 144.

(19) The resin used was prepared from a chloromethyl functionalized JandaJel™ with a loading of approximately 1.5 mmol g^{-1}. Diazo-functionalized resin **2** gave a nitrogen content corresponding to a loading of 1.37 mmol g^{-1}.

has enabled the solution-phase synthesis of previously inaccessible oxazoles.[20] Reaction of **3a** under these conditions gave desired oxazole **4a** (R = Ph) as indicated by IR analysis (ester carbonyl shift to 1713 cm^{-1} and disappearance of N−H, ketone, and amide absorptions). Unfortunately, this reaction was accompanied by side reactions that turned the resin beads dark brown. These impurities remained attached to the resin after washing but were released into solution during cleavage of the oxazole product from the resin (see below). We found that replacement of the PPh_3/I_2 reagent with the commercially available Cl_2PPh_3 adduct gave efficient conversion to product **4a** without the generation of undesirable byproducts. The stage was now set to investigate additional cleavage reactions of oxazole **4** (Scheme 2).[21]

Scheme 2[a]



[a] (a) $LiBH_4$ (5 equiv), $LiEt_3BH$, (10 mol %), THF, 2 h, then AcOH, (unoptimized); (b) NaOMe (20 mol %), MeOH, THF, 16 h; (c) piperidine (8 equiv), $AlCl_3$, (2 equiv), CH_2Cl_2, 16 h, then aqueous Na_2CO_3.

Treatment of oxazole **4a** with a combination of lithium borohydride and lithium triethylborohydride gave the hydroxymethyl oxazole **5**.[22] Ester **6** was obtained by transesterification of **4a** using sodium methoxide in a methanol/THF solution. Finally, an amidation/cleavage reaction was performed by treating **4a** with a mixture of piperidine and aluminum chloride affording amide **7a**.[23] Each of the cleavage reactions was quenched with the appropriate reagent, and these mixtures were passed through a strong acid, strong base mixed-bed ion-exchange resin column before isolation of the products.

Insertion reactions of polymer-bound α-diazo-*β*-ketoester **2** with additional amides were also investigated (Table 1). The amides used contained either a bulky group or electron-rich or electron-poor aromatic substitution. Insertion, cyclodehydration, and cleavage reactions were performed as described above providing an array of oxazoles, **7b**−**g**. The crude products were assessed for purity using HPLC and then isolated as pure compounds for analysis using preparative TLC. Clearly, this solid-phase N−H insertion/cyclodehydration oxazole synthesis tolerates amide substrates with various steric and electronic characteristics. The crude products showed excellent purity, and isolated yields of purified products were moderate.[24]

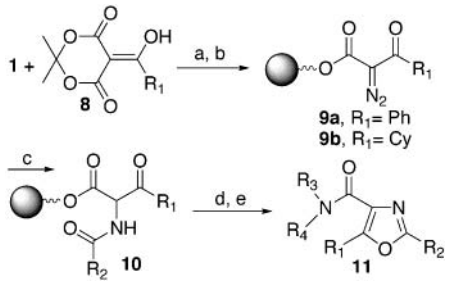
Table 1. Purity and Yield of Oxazoles **7b**−**g**

7	R =	purity[a]/%	yield[b]/%
b	^{t}Bu	78	36
c	*o*-Tol	98	47
d	*m*-MeOPh	92	30
e	*p*-MeOPh	94	22
f	*p*-CF_3Ph	98	35
g	*p*-BrPh	96	29

[a] Purity of crude product assessed using RP-HPLC (254 nm). [b] After purification using preparative TLC.

Finally, a series of compounds that displayed additional diversity at the 5-position of the oxazole ring were synthesized. Resin **1** was first reacted with a set of acyl-Meldrum acid adducts[25] **8** giving the corresponding polymer-bound *β*-ketoesters.[26] Subsequent diazotransfer gave α-diazo-*β*-ketoester resins **9a** and **9b** (Scheme 3). Unfortunately, acyl-Meldrum acid adducts of type **8** are difficult to prepare and isolate in sufficient purity. The preparation of diverse polymer-bound *β*-ketoesters is currently the limiting factor in the preparation of larger oxazole libraries.

Scheme 3[a]



[a] (a) **8** (2.5 equiv), THF, △, 16 h; (b) dodecylbenzenesulfonylazide (5 equiv), Et_3N (5 equiv), toluene, 16 h; (c) primary amide (5 equiv), Rh_2Oct_4 (2 mol %), toluene, 60 °C, 2 h; (d) Burgess reagent (5 equiv), THF, 70 °C, 6 h, (sealed vial); (e) amine (8 equiv), $AlCl_3$ (2 equiv), CH_2Cl_2, 16 h, then aqueous Na_2CO_3.

As expected, resin-bound α-diazo-*β*-ketoesters **9a** and **9b** underwent clean conversion to the N−H insertion products

(20) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604. For other elegant small-ring heterocycle cyclizations from this group, see: Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165, and references therein.

(21) For reactions of 4-substituted-oxazoles, see: Clapham, B.; Richards, A. J.; Wood, M. L.; Sutherland, A. J. *Tetrahedron Lett.* **1997**, *38*, 9061.

(22) (a) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604. (b) Clapham, B.; Sutherland, A. J. *Tetrahedron Lett.* **2000**, *41*, 2253.

(23) (a) Barn, D. R.; Morphy, J. R.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3213. (b) Ley, S. V.; Mynett, D. M.; Koot, W.-J. *Synlett* **1995**, 1017.

(24) All purified compounds were characterized using IR, ^{1}H NMR, and HRMS and gave data in accordance with their structures.

(25) (a) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087. (b) Houghton, R. P.; Lapham, D. J. *Synthesis* **1982**, 452. (c) Sørensen, U. S.; Falch, E.; Krogsgaard-Larsen, P. *J. Org. Chem.* **2000**, *65*, 1003.

(26) Tieze, L. F.; Steinmetz, A.; Balkenhohl, F. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1303.

when treated with an amide and the rhodium catalyst. Cyclodehydration of these more bulky α-(acylamino)-β-ketoesters **10** using the phosphorane/Et_3N reagents proved unreliable yielding incomplete conversion to some products as indicated by IR analysis. Researchers at Novartis recently reported that the Burgess reagent[27] can also be used to prepare oxazoles using the cyclodehydration strategy.[28] When polymer-bound substrates **10** were treated with excess Burgess reagent (5 equiv) at elevated temperatures for 6 h, a clean cyclodehydration to oxazole products was observed. These oxazoles were cleaved from the resin as their dipropyl or morpholine amides **11** and obtained in excellent purity and in slightly superior yields (Table 2) than those prepared using the phosphorane reagents (Table 1).

In conclusion, a highly efficient solid-phase synthesis of oxazoles has been developed. This methodology emphasizes the synthetic utility of polymer-bound diazo substrates. Although the preparation of polymer-supported β-ketoesters has been problematic, we are refining new methodology which we will report in due course. In addition, we are currently investigating other applications of polymer-bound diazo substrates.

(27) Burgess reagent ((methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt) was purchased from Fluka. See also: Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(28) Brain, C. T.; Paul, J. M. *Synlett* **1999**, 1642.

Table 2. Purity and Yield of Oxazoles **11**

	R_1 = Cy; R_3, R_4 = morpholine		R_1 = Ph; R_3 = R_4 = *n*-propyl	
R_2	purity[a]/%	yield[b]/%	purity[a]/%	yield[b]/%
^{t}Bu	86	28	91	36
o-Tol	94	53	99	52
p-MeOPh	92	48	94	39
p-CF_3Ph	90	39	97	53
p-BrPh	94	48	96	50

[a] Purity of crude product assessed using RP-HPLC (254 nm). [b] After purification using preparative TLC.

Acknowledgment. Financial support from the National Institutes of Health (GM-56154), The Scripps Research Institute, The Skaggs Institute for Chemical Biology, and Novartis is gratefully acknowledged. B.C. is a Skaggs Postdoctoral Fellow. We thank Dr. Peter Wirsching for assistance in the preparation of this manuscript.

Supporting Information Available: Experimental procedures and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010075N