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Rhodium Carbenoid N–H Insertion Reactions of Primary Ureas: Solution and Solid-Phase Synthesis of Imidazolones

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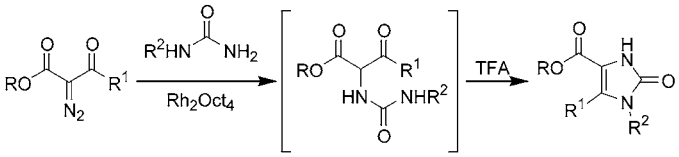
ABSTRACT



The solution and solid-phase synthesis of imidazolones is reported. The key step for the preparation of these compounds is the N–H insertion reaction of primary ureas into highly reactive rhodium carbenoid intermediates. Typically, a soluble or support-bound α-diazo-β-ketoester is treated with a rhodium carboxylate catalyst in the presence of a primary urea to give the corresponding N–H insertion product. Subsequent acid-catalyzed cyclodehydration of these insertion products affords the desired imidazolone products.

Combinatorial chemistry is a widely accepted methodology that is used to generate libraries of molecules for the discovery of biologically active leads and also the optimization of potential drug candidates.[1] The mainstay of combinatorial chemistry is solid-phase organic synthesis (SPOS).[2] Here, the intermediate products are attached to insoluble resins and consequently, workup and purification require only simple washing and filtration procedures. One problem with solid-phase chemistry is that some types of solution-phase reactions do not readily transfer onto the solid-phase format.[3] One class of reactions that has received little attention in solid-phase applications are those of diazo-functionalized substrates.[4] This is surprising since diazo compounds have great utility in synthetic organic chemistry[5] and in light of this, research from our laboratory has shown the potential of these substrates in the solid-phase synthesis of oxazoles[6] and indoles[7] from polymer-bound α-diazo-β-ketoesters.[8]

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(1) (a) Bunin, B. A. *The Combinatorial Index*; Academic Press, Ltd.: London, 1998. (b) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Elsevier Science, Ltd.: New York, 1998. (c) *Combinatorial Chemistry: Synthesis, Analysis, Screening*; Jung, G., Ed.; Wiley-VCH: Weinheim, Germany, 1999. (d) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M., Kerwin, J. F., Jr., Eds.; Wiley & Sons, Ltd.: New York, 1998.

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

(3) For a review of solid-phase reactions, see: Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385.

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

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

(6) Clapham, B.; Spanka, C.; Janda, K. D. *Org. Lett.* **2001**, *3*, 2173.

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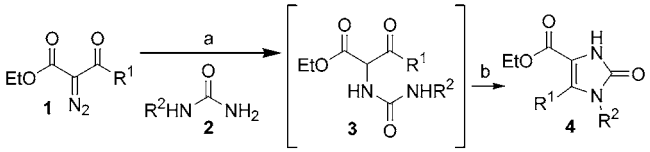
Additionally, several outstanding papers have recently been published that describe the solid-phase synthesis of molecularly diverse compounds using reactions of diazo-functionalized substrates.[9]

Both our oxazole and indole solid-phase syntheses have utilized highly reactive polymer-bound rhodium carbenoid intermediates that are generated by exposure of the corresponding diazocarbonyls with a rhodium carboxylate catalyst. These reactive intermediates readily insert into the N−H bond of primary amides[10] and also into the N−H bond of *N*-alkyl anilines[11] to form products that are converted into the corresponding oxazoles and indoles, respectively. In all cases, these N−H insertion reactions have proven to be efficient; hence, we began a program investigating the use of these insertion reactions with alternative N−H-containing substrates as a means of creating structurally diverse compounds. Reported herein are our findings of rhodium carbenoid N−H insertion reactions of primary ureas.

The imidazolones are 1,3-dinitrogen-containing five-membered heterocycles that are structurally related to imidazole. Since small heterocycles with similar structures are known to exhibit a broad range of biological activity, compounds such as the imidazolones constitute ideal scaffolds for combinatorial evaluation.[12] With this in mind, we postulated that the key imidazolone precursors could be prepared by using an N−H insertion reaction of a primary urea with a suitably activated diazocarbonyl. The preliminary N−H insertion and 2-imidazolone formation reactions were investigated in the solution phase, Scheme 1 and Table 1.

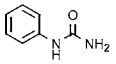
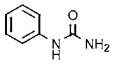
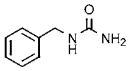
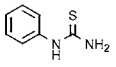
Scheme 1[a]



[a] Reaction conditions: (a) Rh_2Oct_4 (2 mol %), **2** (1.5 equiv), 1:1 toluene/DCE, 80 °C, 30 min. (b) 10% TFA, rt, 30 min.

To optimize the insertion reaction conditions, several variables were investigated before an acceptable method was found. The major problem encountered was the solubility of the urea reaction component. Solvents that were examined included chlorinated hydrocarbons such as 1,2-dichloroethane (DCE) and aromatic hydrocarbons (benzene or toluene). Although these solvents did not fully solubilize the urea substrates **2**, the reaction was still tenable. Polar aprotic solvents such as *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA) were able to fully solubilize ureas **2** but gave poor results in the insertion reaction. To overcome these solubility issues, it was imperative to use finely powdered ureas with vigorous stirring of the reaction to achieve improved yields of product as estimated by TLC. During the optimization experiments, we also found that the manner in which the catalyst was added to the reaction was critical for success. When the catalyst was added in one portion, several unidentified side products were observed by TLC. The best procedure involved preparing a fine suspension of the rhodium octanoate catalyst in toluene using sonication. This suspension of catalyst was slowly added to a vigorously stirred, preheated suspension of the primary urea **2** (1.5 equiv) and the α-diazo-*β*-ketoester **1** over a period of 10 min. Generally, all of the reactions were complete after an additional 20 min of heating. Although the N−H insertion product **3** ($R^1 = R^2 =$ Ph) from this reaction could be isolated and characterized, the best yield obtained was only 34% after purification by chromatography and recrystallization. We postulated that the slightly acidic nature of the silica gel may have been responsible for the conversion of the insertion product **3** into the imidazolone **4** via acid-catalyzed dehydration. To verify this, after the insertion reaction had been allowed to proceed, the solution was cooled to room temperature before the addition of a 10% volume of TFA. Gratifyingly, the desired imidazolones **4** were isolated directly from this two-step, one-pot reaction in excellent yields. The results from these experiments are presented in Table 1. The N−H insertion reactions of a methylguanidine and phenylthiourea were also investigated (Table 1 entries 5 and 6). When the reaction was performed with methylguanidine, consumption of the starting α-diazo-*β*-ketoester

Table 1. Solution-Phase Synthesis of Imidazolones **4**

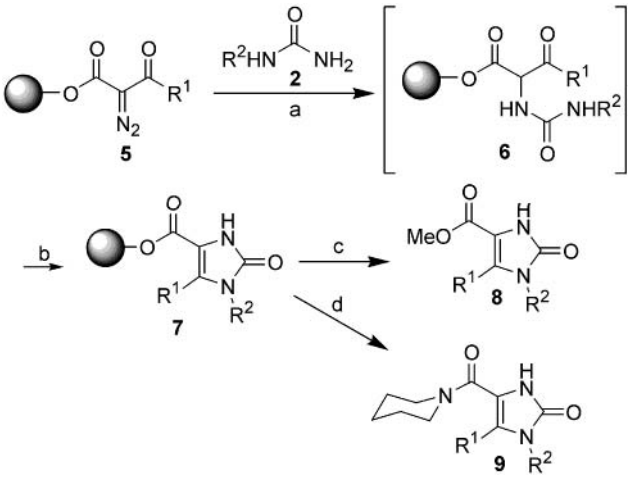
entry	R^1	**2**	yield **4** / %
1	Me		72
2	Ph		85
3	Ph		85
4	Ph		80
5	Ph		-
6	Ph		-

(7) Lee, S.-H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *J. Comb. Chem.* In press.
(8) Clapham, B.; Lee, S.-H.; Koch, G.; Zimmermann, J.; Janda, K. D. *Tetrahedron Lett.* **2002**, *43*, 5407.
(9) (a) Savinov, S. N.; Austin, D. J. *Org. Lett.* **2002**, *4*, 1419. (b) Yamazaki, K.; Kondo, Y. *Chem. Commun.* **2002**, 210. (c) Nagashima, T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2001**, *123*, 2695.
(10) Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 591.
(11) Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J.; Muthusamy, S.; Swann, E. *J. Chem. Soc., Perkin Trans. 1* **2002**, *14*, 1672.
(12) There is currently one reported example of a solid-phase imidazolone synthesis: (a) Cheng, J.-F.; Kaito, C.; Chen, M.; Arrhenius, T.; Nadzan, A. *Tetrahedron Lett.* **2002**, *43*, 4571. For the solid-phase synthesis of related imidazolidones, see: (b) Nefzi, A.; Ostrech, J. M.; Giulanotti, M.; Houghten, R. A. *J. Comb. Chem.* **1999**, *1*, 195. (c) Goff, D.; *Tetrahedron Lett.* **1998**, *39*, 1477.

1 was observed; however, no N−H insertion product could be isolated from the reaction. When phenylthiourea was used, both starting materials were isolated unchanged even after heating for extended periods.

On the basis of the successful results in solution, the solid-phase version of the primary urea insertion reaction was also investigated, Scheme 2. Here, the hydroxypentyl-*Jand*a*Jel*[7,13]

Scheme 2[a]

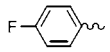
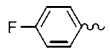
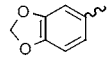
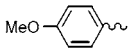
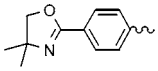
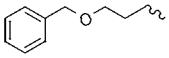
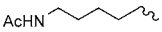


[a] Reaction conditions: (a) Rh_2Oct_4 (2 mol %), **2** (3 equiv), 1:1 toluene/DCE, 80 °C, 30 min. (b) 10% TFA, rt, 30 min. (c) NaOMe (2.5 equiv), 4:1 THF/MeOH, 50 °C, 1 h. (d) Piperidine (10 equiv), $AlMe_3$ (5 equiv), toluene, 50 °C, 16 h.

polymer-bound α-diazo-*β*-ketoester[8] **5** was allowed to react with 3 equiv of urea **2** under conditions similar to those developed in the solution phase. The progress of this reaction was easily monitored by IR (disappearance of the C═N═N stretch at ∼2140 cm^{-1}, and the conversion to the desired urea insertion product was confirmed by the appearance of urea carbonyl and NH stretches at ∼1650 and 3360 cm^{-1}, respectively). Treatment of resin-bound insertion product **6** with 10% TFA at room temperature afforded the resin-bound imidazolone **7** within 1 h, as determined by IR (disappearance of the NH stretch at ∼3360 cm^{-1}, ketoester absorptions at ∼1740 and ∼1690 cm^{-1}, and urea carbonyl absorptions at ∼1650 cm^{-1} and the appearance of a strong carbonyl absorption at ∼1700 cm^{-1} corresponding to both the α,*β*-unsaturated ester and the cyclic urea). The polymer-bound imidazolones **7** were then cleaved from the resin by trans-esterification to give esters **8** or by a diversity-building amidation reaction[14] to give amides **9**. After cleavage, crude products **8** and **9** were passed through a filtration cartridge containing either a strong acid (esters **8**) or mixed bed ion-exchange resins (amides **9**) to remove excess reagents before being analyzed for purity using HPLC. Finally, each of the crude products **8** and **9** were further purified using preparative TLC to give final isolated yields of product based upon the loading of resin **5**.

To investigate the scope of this reaction and establish its tolerance of different substrates, a pilot library was prepared using eight α-diazo-*β*-ketoesters **5** and five ureas **2** (Tables 2 and 3).

Table 2. Solid-Phase Synthesis of Imidazolones **8** and **9** (R^2 = Ph)

entry	R^1	product	purity[a] / %	yield[b] / %
1		**8**	87	79
2		**9**	94	84
3		**8**	92	54
4		**8**	75	45
5		**8**	79	51
6		**8**	94	51
7		**9**	92	53
8		**8**	72	19
9		**8**	-	-

[a] Purity of crude product assessed using HPLC (254 nm). [b] Yield of pure product after isolation using preparative TLC.

The results presented in Table 2 were obtained using phenylurea **2** (R^2 = Ph) and various α-diazo-*β*-ketoesters **5** containing electronically and chemically diverse substituents (R^1). As shown in Table 2, this reaction sequence provided the desired products in respectable yields and high purity. The only exception was the product bearing long alkyl R^1 substituents (entries 8 and 9), presumably due to the competing intramolecular C−H insertion as a possible side reaction.[5,15] Data provided in Table 3 was obtained using electron-rich and electron-deficient aryl, benzyl, and alkyl primary ureas, and each substrate gave modest to good yields of product. It is noted that no evidence for the competing insertion into the secondary urea N−H group was observed.

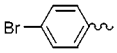
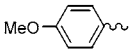
The final part of this study was the introduction of an additional substituent onto the aryl imidazolone **10** using a Suzuki coupling reaction[16] (Scheme 3). Here, incubation of **10** with phenyl boronic acid and palladium catalyst followed

(13) *Jand*a*Jel* resins are available from Aldrich Chemical Co. (a) 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. For recent applications, see: (b) Brummer, O.; Clapham, B.; Janda, K. D. *Tetrahedron Lett.* **2001**, *42*, 2257. (c) Clapham, B.; Cho, C.-W.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 868.

(14) (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.

(15) C−H insertion reactions of α-diazo-*β*-ketoesters are documented: (a) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223. (b) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

Table 3. Solid-Phase Synthesis of Imidazolones **8** (R^1 = 4-CF_3Ph)

entry	R^2	purity[a] / %	yield[b] / %
1		93	58
2		80	57
3		35	16
4		97	58
5		94	59

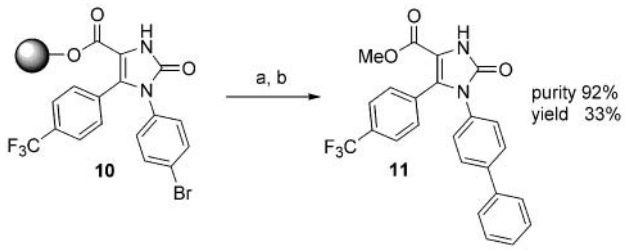
[a] Purity of crude product assessed using HPLC (254 nm). [b] Yield of pure product after isolation using preparative TLC.

by transesterification cleavage gave the crude imidazolone **11** in 92% purity and in 33% yield after purification by preparative TLC.

In summary, we have developed a highly efficient two-step, one-pot procedure for the synthesis of imidazolones in solution. The first step involves a novel N−H insertion reaction of a primary urea into an α-diazo-β-ketoester-derived rhodium carbenoid. This insertion product rapidly ring closes to form the desired imidazolone product by brief treatment with acid. This chemistry readily translates onto insoluble polymer resins and has been utilized to prepare a small array of imidazolones. The chemistry of other polymer-bound carbonyls and insertion reactions is currently under further investigation in our laboratory, and these results will be reported in due course.

(16) Wu, T. Y. H.; Ding, S.; Gray, N. S.; Schultz, P. G. *Org. Lett.* **2001**, *3*, 3827.

Scheme 3[a]



[a] Reaction conditions: (a) Phenylboronic acid (10 equiv), K_3PO_4 (10 equiv), Pd(dppf)Cl_2 (20 mol %), dioxane, 90 °C, 24 h. (b) NaOMe (2.5 equiv), 4:1 THF/MeOH, 50 °C, 1 h.

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Supporting Information Available: Representative procedures and spectral characterization of all compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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