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Solid-phase synthesis of oxazolones and other heterocycles via Wang resin-bound diazocarbonyls

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Abstract—The preparation of Wang resin bound α-diazo-β-ketoesters is described. These highly useful intermediates were used for the synthesis of a series of heterocycle libraries, which were obtained from the resin using TFA cleavage. In addition, a novel route for the synthesis of oxazolones using an N–H insertion strategy is disclosed.

1. Introduction

Combinatorial and parallel synthetic methodology provides the main driving force for the preparation of compound libraries for application in lead discovery and high throughput medicinal chemistry research within the pharmaceutical industry.[1] Many different formats of high throughput chemistry are available and solid-phase organic synthesis (SPOS) plays a pivotal role given the convenient handling of large numbers of synthetic intermediates.[2] However, SPOS is not without its drawbacks since there is often extended development times required to optimize new solid-phase chemical reactions.

Research from our own group has harnessed the synthetic utility of diazocarbonyl compounds[3] in order to prepare a plethora of biologically privileged 'lead-like' scaffolds. This program has centered on the application of polymer-bound α-diazo-β-ketoesters[4] as key building blocks for the diversity-oriented synthesis (DOS)[5] of a series of heterocycle libraries, including oxazoles,[6] indoles,[7] imidazolones and imidazoles,[8] and pyrazinones and pyrazines.[9]

This work relied upon a hydroxypentyl *J*anda*J*el resin[10] as the support for the polymer-bound α-diazo-β-ketoesters; this support is very robust and transesterification or Lewis acid-assisted amidation[11] cleavage reactions were used to obtain the products from the support, rather than trifluoroacetic (TFA) acidolysis, which is commonly employed when using classical linker strategies.[12]

During our studies preparing heterocycles using N–H insertion strategies, we found that phenyl carbamate **2** is an excellent coupling partner when reacted with diazocarbonyls (Scheme 1). Moreover, treatment of this intermediate **3** with mild base afforded the ring-closed oxazolone products **4**. However, when this chemistry was applied to a solid-phase approach, the aluminum amide cleavage conditions failed to give the desired oxazolone products, and only the ring-opened urea products **5** were formed. Although we have been able to develop the chemistry of the urea formation to give highly useful methodology,[13] we were still intrigued with the prospect of preparing libraries of oxazolones given their potential to yield compounds of biological significance.[14]

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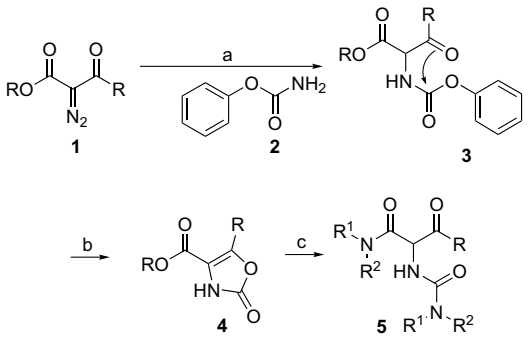


Scheme 1. Reagents and conditions: (a) Rh_2Oct_4 (2 mol %), **2** (3 equiv), toluene–dichloroethane 1:1, 80 °C, 1 h; (b) $^{i}Pr_2EtN$ (3 equiv), toluene, reflux, 6 h; (c) R^1R^2NH (3 equiv), $AlMe_3$ (3 equiv), toluene, 100 °C, 16 h.

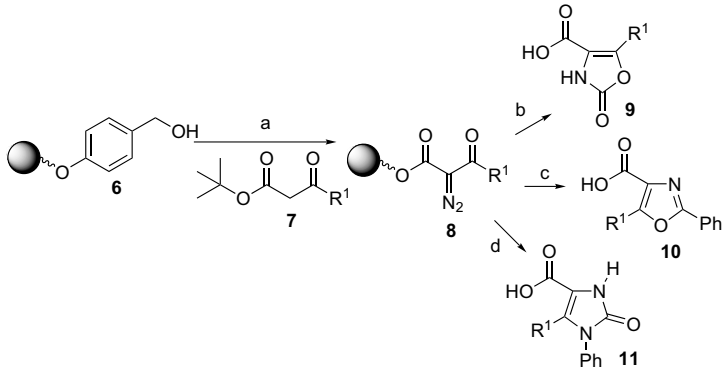
Table 1. Solid-phase synthesis of heterocycles from **8**

R^1	**9** Purity[a] (yield)[b]	**10** Purity[a] (yield)[b]	**11** Purity[a] (yield)[b]
Me	99 (43)	96 (47)	99 (61)
$BnO(CH_2)_3$	76 (18)	86 (22)	62 (11)
$^{t}BuO(CH_2)_3$	96 (31)[c]	85 (23)[c]	99 (28)[c]
$AcNH(CH_2)_5$	98 (49)	[d]	[d]
	59 (25)	24 (5)	26 (4)
Ph	88 (20)	39 (12)	68 (37)

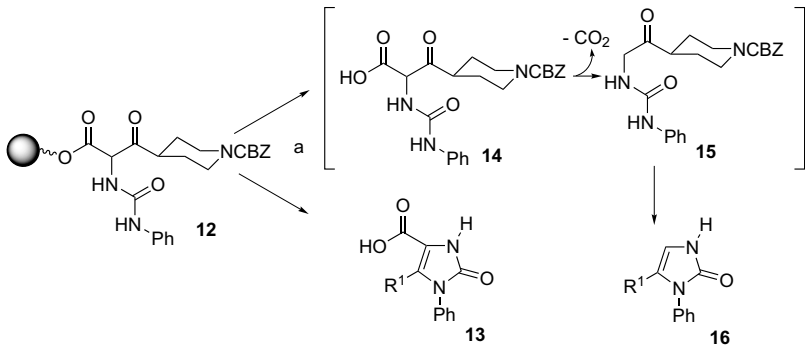
[a] Purity assessed by HPLC at 254 nm.
[b] Yield of product after purification by preparative HPLC; yield based upon loading of **8**.
[c] ^{t}Bu group removed during cleavage.
[d] Complex mixture of products.

In light of the incompatibility of the Lewis acid-assisted amidation reaction with the oxazolone scaffolds, an alternative linker strategy was sought. Wang resin bound substrates were investigated and found to be ideal substrates for oxazolones carboxylic acid synthesis. The Wang bound β-ketoesters were synthesized using a transesterification reaction. A mixture of Wang resin **6** and ^{t}Bu-β-ketoesters **7** was heated to reflux in toluene, after washing, standard diazotransfer conditions provided the corresponding Wang resin-bound α-diazo-β-ketoesters **8**. Next, the key building blocks **8** were treated with phenyl carbamate **2** in the presence of rhodium octanoate catalyst to give the N–H insertion products that were treated sequentially with $^{i}Pr_2EtN$ and TFA to provide oxazolones **9**.[15] Key building blocks **8** were also used to synthesize a series of oxazoles **10** and imidazolones **11** using an N–H insertion/cyclodehydration strategy (Scheme 2).[16] For the oxazole synthesis, a primary amide was used as the insertion component, the heterocycle ring was closed using Burgess reagent, and the oxazoles **10** were obtained by cleavage with TFA. In the case of the imidazolones, a primary urea was used as the insertion component, the product from this reaction was treated with TFA to achieve both cyclization to the imidazolone and cleavage from the resin in one pot. Each of the oxazolones **9**, oxazoles **10**, and imidazolones **11** cleavage products were assessed for crude purity by HPLC and then purified by preparative HPLC. The results from this study are presented in Table 1.

In the case of the oxazolones **9**, the majority of the desired products were isolated in excellent purity and good yield. When ^{t}Bu protected alcohols were employed, each of the products were obtained as the deprotected alcohols. In addition, when benzyl ether and benzyl carbamate (CBZ) protected side groups were employed, slightly inferior purities and yields were obtained for the desired cleavage products, presumably because of their premature cleavage during prolonged exposure to neat TFA. Finally, an interesting finding was observed during the cleavage/cyclization of one of the imidazolones (Scheme 3). In this case, the major cleavage product was imidazolone **16** (19%) rather than imidazolone acid **13** (4%); the cyclization reaction can occur both prior to and after cleavage from the resin. However, in the latter case, the β-ketoacid cleavage product **14** can undergo acid catalyzed decarboxylation to give ketourea **15** before ring closure to imidazolone **16**.



Scheme 2. Reagents and conditions: (a) (i) **7** (3 equiv), toluene, reflux, 16 h; (ii) dodecylbenzenesulfonyl azide (3 equiv), Et_3N (3 equiv), toluene, 24 h; (b) (i) Rh_2Oct_4 (2 mol %), **2** (3 equiv), toluene, 70 °C, 1 h; (ii) $^{i}Pr_2EtN$ (3 equiv), toluene, reflux, 6 h; (iii) TFA, rt, 3 h; (c) (i) Rh_2Oct_4 (2 mol %), $PhCONH_2$ (3 equiv) toluene–dichloroethane 1:1, 80 °C, 1 h; (ii) Burgess reagent (3 equiv), THF, μw, 100 °C, 10 min; (iii) TFA, rt, 3 h; (d) (i) $PhNHCONH_2$ (3 equiv) toluene–dichloroethane 1:1; 80 °C, 1 h; (ii) TFA, rt, 3 h.



Scheme 3. Reagents and conditions: (a) TFA, rt 3 h.

2. Conclusions

In summary, a novel and efficient N–H insertion strategy for the synthesis of oxazolones from diazocarbonyls has been devised. Additionally, in order to synthesize oxazolone arrays using solid-phase synthetic methodology, an alternative TFA labile linker strategy was developed; the Wang resin-bound diazocarbonyl substrates were also shown to be of great utility in the preparation of oxazoles and imidazolones.

Acknowledgements

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15. *Polymer-bound α-diazo-β-ketoester* **8**. A 100 mL recovery flask was charged with Wang resin (Polymer Labs, 5.00 g, ~5.0 mmol), ^{t}Bu–acetoacetate (2.37 g, 15.0 mmol), and toluene (75 mL). The mixture was heated to reflux for 6 h, and the product collected in a fritted syringe and washed with toluene. Dodecylbenzenesulfonyl azide (8.79 g, 25 mmol) and Et_3N (3.49 mL, 25 mmol) were added, and the resultant mixture was shaken for 24 h. Washing with DMF, THF, ether, and hexanes gave **8** white powder; yield 100%; Elemental Analysis: N = 2.56%; loading 0.914 mmol/g; IR (cm^{-1}) 2137, 1713, 1657.
Phenyl carbamate insertion. A round bottomed flask was charged with resin **8** (R^1 = Me, 600 mg, 0.55 mmol), phenyl carbamate **2** (226 mg, 1.65 mmol), purged with argon and then a toluene (8 mL) was added. The mixture was heated to 80 °C and a suspension of Rh_2Oct_4 (~9 mg, 2 mol %) in toluene (2.0 mL) was added over 10 min. Nitrogen effervescence was observed and stirring was continued for 1 h, before the product was collected by filtration and washed with DMF, THF, $CHCl_3$, ether, and hexanes. Pale brown powder; IR (cm^{-1}) 1725 (broad peak).
Oxazolone formation. A round bottomed flask was charged with insertion product (580 mg), toluene

(11 mL) and Hunigs base (870 μL, 5.00 mmol). The resulting mixture was heated to reflux for 6 h, and the polymer-bound oxazolone product was collected by filtration and washed with DMF, MeOH, THF, $CHCl_3$, ether, and hexanes. Pale brown powder; IR (cm^{-1}) 1774, 1718. *Cleavage of oxazolones* **9**. The polymer-bound oxazolone was treated with TFA (6.0 mL) and shaken for 3 h. The product was collected and the resin washed with TFA (3 × 6.0 mL). After concentration by evaporation, the crude product **9** was assessed for purity using HPLC, and then purified by preparative HPLC. Crude purity 99%; Isolated yield 43%; white powder; mp 202–204 °C; IR (cm^{-1}) 3058, 2840, 1789, 1747, 1668, 1651; ^1H NMR (500 MHz, CD_3OD): δ 2.36 (3H, s); ^{13}C NMR (125 MHz, CD_3OD): δ 11.7, 116.7, 147.5, 156.3, 161.8; HRMS *m/z* 142.0147 $[M-H]^-$, calcd for $C_5H_4NO_4$ 142.0146.

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