Pergamon

Tetrahedron Letters 43 (2002) 5407–5410

TETRAHEDRON LETTERS

The preparation of polymer bound β-ketoesters and their conversion into an array of oxazoles

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Received 18 April 2002; revised 5 June 2002; accepted 7 June 2002

Abstract—A series of diverse polymer bound β-ketoesters have been prepared using a transesterification reaction between *t*-butyl β-ketoesters and a hydroxybutyl functionalized *J*anda*J*el resin. Additionally, these highly useful polymer bound substrates have also been prepared using a transesterification reaction with commercially available methyl or ethyl β-ketoesters using lithium perchlorate as a catalyst. The polymer bound β-ketoesters were then converted into the corresponding α-diazo-β-ketoesters using standard diazo transfer conditions and these products were utilized in the synthesis of an array of oxazoles. © 2002 Elsevier Science Ltd. All rights reserved.

The preparation of diverse libraries of organic compounds is an important facet of modern drug discovery programs. The use of combinatorial chemistry has accelerated the production of such libraries,[1] and many of the techniques developed to do this have also been applied in the discovery of new catalysts and materials of interest.[2] One of the most commonly employed methods in library production is solid phase organic synthesis (SPOS).[3] In this approach, the desired starting materials are attached onto an insoluble polymer. Since purification is facilitated by simple filtration, subsequent building blocks and reagents can be added in excess in order to drive reactions to completion.

Oxazoles are a class of heterocyclic compounds that are believed to occur in nature from post-translational modification of serine and threonine residues in peptides.[4] There is currently a large interest in developing new methodology for the preparation of oxazoles since this heterocycle nucleus is present in several structurally complex and biologically active natural products.[5] Recently, we reported the solid phase synthesis of oxazoles.[6] In this approach, polymer bound α-diazo-β-ketoesters were decomposed using a rhodium catalyst to form a highly reactive rhodium carbenoid intermediate that reacts with a primary amide to form the corresponding N–H insertion product.[7] These α-acylamino-β-ketoester insertion products were then converted into oxazoles using a Burgess' reagent mediated cyclodehydration reaction.[8]

One major problem encountered during this work was the preparation of polymer bound β-ketoesters. We were particularly interested to see a recent report whereby microwave irradiation has been used to affect the loading of β-ketoesters on to hydroxy functionalized resins using a transesterification reaction.[9] Reported herein are our findings in the preparation of these highly useful polymer bound intermediates.

The support used for our synthesis was a hydroxybutyl functionalized *J*anda*J*el resin,[10] prepared according to literature precedent.[11] In our original work, the polymer bound β-ketoesters were prepared by reaction of this resin with acyl-Meldrums acid adducts.[12] Unfortunately, these Meldrums acid adducts proved very difficult to prepare, isolate and store and alternative procedures were sought. We found that heating the resin in the presence of *t*-butyl acetoacetate ($R_1 = Me$) in toluene at reflux[13] for 6 h (Table 1, method a) afforded the desired polymer bound acetoacetate. When the same conditions (3 equiv., toluene reflux, 6 h) were employed using ethyl or methyl acetoacetate, the rate of conversion was considerably slower than with the *t*-butyl β-ketoester. However, when 20 mol% lithium perchlorate catalyst[14] was added to this reaction (Table 1, method b), good conversions were observed as estimated by IR (disappearance of OH at $\sim$3350 cm^{-1} and appearance of ester and ketone carbonyls at $\sim$1740 and 1715 cm^{-1}, respectively) (note: extensive

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PII: S0040-4039(02)01076-6

washing with DMF was required to remove residual catalyst from the resin) (Scheme 1).

The preparation of more diverse polymer bound β-ketoesters was also explored (Table 1). Since the commercial availability of diverse β-ketoesters is very limited, a series of *t*-butyl β-ketoesters were first prepared from mono *t*-butyl malonate according to literature precedent.[15] Included in this group of substituents were electron-rich and electron-deficient aromatics, pyridines, heterocycles, benzyl and *t*-butyl ethers, BOC, CBZ and acyl-protected amines, and the oxazoline-protected acid. To compare the two different procedures, several commercially available methyl or ethyl β-ketoesters were also used to prepare the polymer bound products. After conversion, the polymer bound products were then treated under standard diazo transfer conditions to provide an array of polymer bound α-diazo-β-ketoesters **3**. Each of the products, **3**, was analyzed for nitrogen content using elemental analysis and these results enabled the loading of each product **3** to be calculated. In total, 24 polymer bound α-diazo-β-ketoesters were prepared in an average yield of 87% based upon original hydroxyl loading of resin **1**. We note that the *t*-butyl β-ketoesters gave slightly better conversion (method a; 17 examples, av. 90%) vs methyl and ethyl ketoesters (method b; 7 examples, av. 81%).

With a large array of polymer bound α-diazo-β-ketoesters **3** in hand, their conversion into a small array of oxazoles was examined (Scheme 2). In our original work, 5 equiv. of the primary amide **4** and 2 mol% rhodium octanoate catalyst were used. We have since found that these amounts can be reduced to only 3 equiv. and 1 mol%, respectively, with a reaction time of only 1 h in toluene at 65°C without reducing the efficiency this reaction. Each of the polymer bound α-diazo-β-ketoesters, **3**, was reacted with benzamide **4** under these optimized conditions to provide the corresponding α-acylamino-β-ketoesters **5** in good yield based upon mass balance and IR analysis (disappearance of diazo peak at $\sim$2140 cm^{-1}, and appearance of amide carbonyl and NH stretch at $\sim$1660 and 3400 cm^{-1}, respectively). The only exceptions were the β-ketoesters containing pyridyl (Table 1, entries 20 and 21) and α-amino acid substituents (entries 13 and 15). In the case of the pyridyls, the insertion reaction was slow; however, the desired products were formed after heating at 65°C overnight. In the case of the α-amino acid derived substrates, IR analysis indicated disappearance of the diazo group, however, no increase in the mass of the product was observed. It appears that the intramolecular insertion into the carbamate N–H bond occurs preferentially over the intermolecular reaction and a cyclized product is formed.[16]

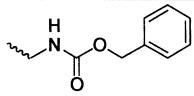
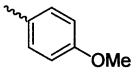
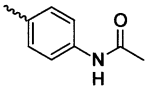
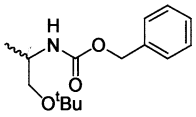
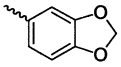
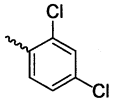
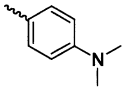
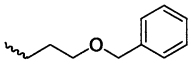
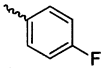
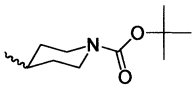
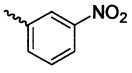
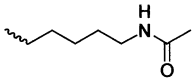
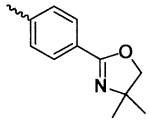
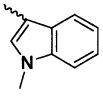
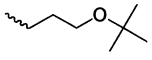
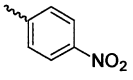
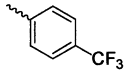
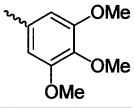
The cyclodehydration of the α-acylamino-β-ketoesters **5** into the corresponding oxazole products **6** has also proved to be a troublesome reaction. The first conditions[8] examined were Burgess' reagent (5 equiv.) in THF under microwave irradiation for 15 min at 130°C. These conditions only worked well for alkyl functionalized substrates (estimated by IR, disappearance of NH stretch, amide and ketone carbonyls, and shift of ester carbonyl to $\sim$1710 cm^{-1}), however, the remaining substrates failed to give complete conversion to product **6**.

In recent work, Novartis reported that dehydration reactions using a polymer supported version of the Burgess reagent were more effective when the triethylamine substituent of the reagent was replaced with dimethylaminopyridine (DMAP).[17] In order to establish if base additives could improve this reaction, the cyclization of **5** (Table 1, entry 2: R_1 = 4-MeOPh) using only 1.5 equiv. of Burgess reagent in the presence of 3 equiv. of base additive (μw, 130°C, THF, 15 min) was investigated. The additives examined were DMAP, diazabicyclo[5.4.0]-undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]-octane (DABCO), pyridine, 2-*t*-butyl-1,1,3,3-tetramethylguanidine (Bartons' base), phosphazene base (P4), 1,8-bis(dimethylamino)naphthalene (Proton sponge) and *N*,*N*-dimethylaniline. Only pyridine gave any considerable improvement over the background reaction (performed without additive) and was elected for further investigation.

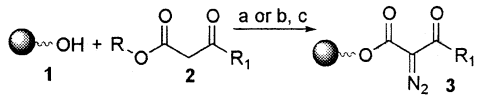
Next, the quantity of pyridine additive used in the reaction was examined. Thus, 3 equiv. of Burgess' reagent were used (μw, 130°C, THF, 15 min) and pyridine was included in various amounts (1, 3, 20 equiv. and as a neat solvent). When the amount of pyridine used was increased from 1 to 20 equiv., an increased conversion to oxazole product **6** was observed, however, running the reaction in neat pyridine gave no advantage over using just 20 equiv. The effect of different solvents for the reaction was also investigated. Dimethylacetamide (DMA), dimethylformamide (DMF) and dimethylsulfoxide (DMSO) gave no conversion to product, whereas dichloroethane gave a similar degree of conversion of **5** to **6**, when compared with THF. The best solvents for this reaction were toluene and chlorobenzene, with the latter being slightly superior. Finally, the effect of reaction time and temperature were examined. Using the best conditions (3 equiv. Burgess' reagent, 20 equiv. pyridine, chlorobenzene, μw, 15 min), the reaction temperature was varied between 100, 120, 140, 160 and 200°C. The best results were observed at 100°C. Increasing the temperature gave lower conversions to product **6** and when this reaction was run at 200°C, no conversion was observed.

We have postulated that since the Burgess' reagent is very sensitive to heat, the use of higher temperatures leads to the premature decomposition of the reagent and as a consequence, reduced conversions are observed. With this in mind, the final conditions investigated utilized conventional heating at 80°C. Here, 2 equiv. Burgess' reagent and 10 equiv. of pyridine were added and the reaction was heated for 2 h. After this time, additional Burgess' reagent and pyridine (2 and 10 equiv., respectively) were added and the reaction was heated for another 2 h. These conditions proved to be successful and were used to convert all of the α-

Table 1.

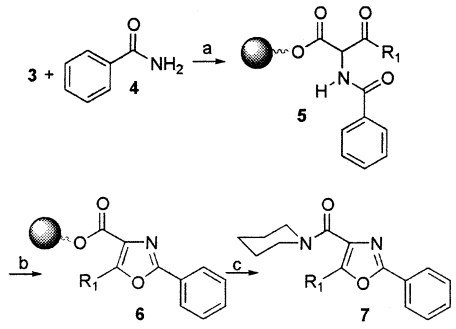
Entry	R_1	Method	Yield **3** / %[c]	Yield **7** / %[d, e]	Entry	R_1	Method	Yield **3** / %[c]	Yield **7** / %[d, e]
1		a	79	42 (85)	13		a	100	0
2		a	93	48 (91)	14		a	100	45 (84)
3		a	77	0	15		a	94	0
4		a	92	62 (96)	16		a	100	18 (50)
5		a	85	17[f]	17		b	72	52 (94)
6		a	98	38 (88)	18		b	76	41 (87)
7		a	90	55 (97)	19		b	77	24 (43)
8		a	91	0	20		b	88	28[f]
9		a	90	38 (70)	21		b	83	17[f]
10		a	84	22 (55)	22		b	73	n/d (78)
11		a	86	35 (96)	23		b	100	29 (35)
12		a	92	31 (44)	24		b	72	50 (86)

[a] Prepared from *t*-butyl β-ketoesters.
[b] Prepared from ethyl or methyl β-ketoesters in the presence of $LiClO_4$.
[c] Yield of **3** estimated using elemental analysis, based upon hydroxyl loading of **1**.
[d] Yield of pure product after isolation using preparative TLC (based upon loading of **3**).
[e] Purity of crude product given in parentheses was estimated by HPLC at 254 nm.
[f] Product passed through only strong basic ion exchange resin prior to purification.



Scheme 1. *Reagents and conditions*: (a) R = ^{t}Bu, toluene, reflux, 6 h; or (b) R = Me or Et, $LiClO_4$ (0.20 equiv.), toluene, reflux, 6 h; (c) dodecylbenzenesulfonyl azide (3 equiv.), Et_3N (3 equiv.) toluene, rt, 16 h.

acylamino-β-ketoester intermediates **5** into the desired oxazole products **6** in good to excellent conversions as estimated by IR. A general trend of reactivity of substrates **5** was observed; the alkyl functionalized substrates were most easily converted into the corresponding oxazoles and the electron-deficient substrates were also smoothly converted into desired



Scheme 2. *Reagents and conditions*: (a) **4** (3 equiv.), $Rh_2(Oct)_4$ (0.01 equiv.), toluene, 65°C, 1 h; (b) [Burgess' reagent (4 equiv.), pyridine (20 equiv.) added in two portions], chlorobenzene, 80°C, 4 h; (c) $AlCl_3$ (2 equiv.), piperidine (6 equiv.), CH_2Cl_2, rt, 16 h.

product. However, the electron-deficient aryl functionalized substrates (Table 1, entries 12, 16, 19 and 23) were the most difficult to convert into product and this in turn provided products with slightly lower yields and purity after cleavage from the resin (vide infra).

After cyclization, the polymer bound oxazoles **6** were cleaved from the resin using a diversity building amidation reaction[18] to give the oxazole amides **7** (Scheme 2). Each of the crude products were passed through a mixed bed ion exchange resin followed by a small pad of Florisil and analyzed for purity using HPLC. The products were then further purified using preparative TLC to give final isolated yields based upon the loading of the polymer bound α-diazo-β-ketoesters **3** (Table 1). As Table 1 clearly shows, most of the products were isolated in reasonable yields and displayed excellent purity, the only exceptions being products bearing electron-deficient aryl groups. It is also noted that the amide functionality in the substrate (Table 1, entries 3 and 8) is not tolerated during either the cyclization or cleavage reaction and no product was isolated from the resin.

In summary, we have shown that a transesterification reaction using *t*-butyl β-ketoesters is the most efficient method for the generation of synthetically useful polymer bound β-ketoesters. These substrates were converted into the corresponding polymer bound α-diazo-β-ketoesters that were used as substrates in rhodium catalyzed primary amide N–H insertion reactions. In addition, optimal conditions for the conversion of the products from these N–H insertion reactions into the corresponding oxazoles have been established. Further studies involving polymer bound α-diazo-β-ketoesters are ongoing in our laboratory and will be reported in due course.

Acknowledgements

We gratefully acknowledge financial support from the National Institutes of Health (GM-56154), The Scripps Research Institute, The Skaggs Institute for Chemical Biology and Novartis Pharma AG, Basel, Switzerland. We also thank Dr. Carsten Spanka (Novartis Pharma AG) for helpful discussions. B.C. is a Skaggs postdoctoral fellow. S.-H.L. acknowledges the Korea Science and Engineering Foundation (KOSEF) for a postdoctoral fellowship.

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