Report

Solid-Phase Synthesis of Substituted Benzazepines via Intramolecular Heck Cyclization

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Solid-Phase Synthesis of Substituted Benzazepines via Intramolecular Heck Cyclization[1]

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The design of cyclic scaffolds which allow the incorporation of a variety of substituents has emerged as an attractive strategy for the generation of combinatorial libraries.[2] We have recently demonstrated the utility of solid-supported allyl and propargyl glycine derivatives in an approach to novel bicyclic amino acid derivatives via the Pauson−Khand reaction.[3] As part of our continued interest in the development of new scaffolds for combinatorial chemistry, we have again exploited these versatile amino acids as substrates for intramolecular Heck cyclizations.

The intramolecular Heck reaction has been well-established as a powerful tool for the construction of complex polycyclic ring systems in the context of natural product synthesis.[4] This process has also been adapted in the solid-phase syntheses of isoquinolinones,[5a] indoles[5b,c] and oxindoles,[5d] benzofurans,[5c] and macrocyclic peptide derivatives.[5e] We recognized that in addition to their utility in the Pauson−Khand reaction, allyl and propargyl glycine derivatives would also be excellent candidates for an intramolecular Heck cyclization. One such approach is shown in Scheme 1, where palladium-catalyzed 7-exo cyclization of 2-iodobenzene-tethered allyl or propargyl glycines would lead to the corresponding functionalized benzazepines. While there have been several recently reported examples of benzazepines prepared by Heck cyclization of an aryl halide with an appended alkene,[6] 7-exo cyclization onto a tethered alkyne is less common.[7] Described herein are solution- and solid-phase approaches to these bicyclic amino acids which demonstrate the utility of this methodology for combinatorial library generation.

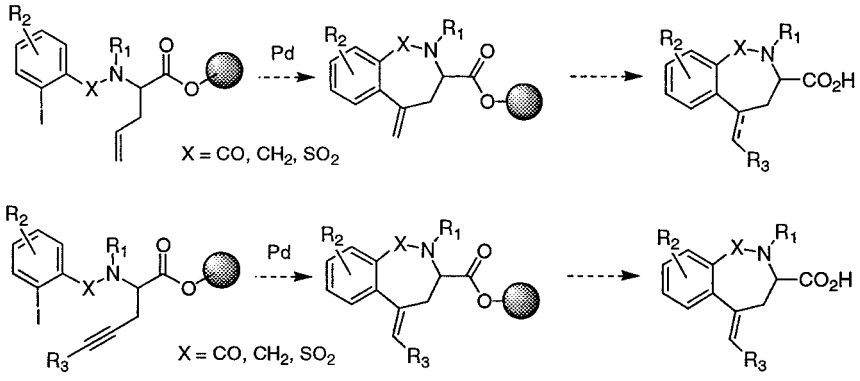
A simple model system was first examined in solution. Reaction of 2-iodobenzoyl chloride with allylglycine methyl ester (**1**) provided benzamide **2** as shown in Scheme 2. N-Methylation afforded the desired cyclization precursor **3** in 89% yield. Treatment of **3** with $Pd(OAc)_2$ (5 mol %) in degassed dimethylformamide (DMF) in the presence of PPh_3, Bu_4NCl, and KOAc at 70 °C for 2 h provided the bicyclic lactam **4** (55%). No evidence of isomerization of the exocyclic alkene was detected by ^1H NMR. N-Alkylation was found to be necessary to prevent facile azlactone formation which occurred upon attempted cyclization of **2**.

With no further optimization, this process was extended to the solid phase as shown in Scheme 3. A solid-phase Fukuyama[8c] protocol was utilized for N-alkylation. Thus, Wang resin-linked fluorenylmethoxycarbonyl (FMOC)-allylglycine **5**[3] was converted to nitrobenzenesulfonamide **6**. Subsequent N-methylation in the presence of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)[8a] afforded **7**, which underwent smooth conversion to the cyclization precursor **8** via a standard deprotection/acylation sequence. Heck cyclization under similar conditions (20 mol % $Pd(OAc)_2$, 5 h) provided **4** in 67% overall yield following cleavage with trifluoroacetic acid (TFA) and esterification.

A second sequence (Scheme 4) was developed to allow access to a larger pool of building blocks for attachment to the amino acid nitrogen. Following deprotection of **5**, reductive amination with benzaldehyde cleanly produced the desired secondary amine **10**. It was found that a two-step protocol, first using the procedure of Look and co-workers[9] for imine formation followed by reduction with sodium triacetoxyborohydride, gave the cleanest and most reproducible results. Subsequent acylation with 2-iodobenzoyl chloride provided **11**, which underwent efficient Heck cyclization as before to bicyclic lactam **13** following acidic cleavage and esterification. Methods for functionalization of the alkene moiety both before and after the cyclization are currently being explored.

An alternative approach (Scheme 5) in which another substituent may be installed prior to cyclization was then examined in solution. This sequence features a Sonogashira arylation[10] of the alkyne terminus, an efficient and dependable method for carbon−carbon bond formation which had been utilized extensively in our earlier work.[3] Acylation of

Scheme 1



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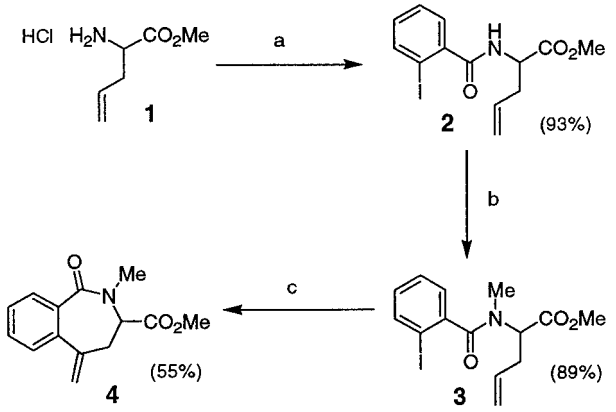
Scheme 2[a]

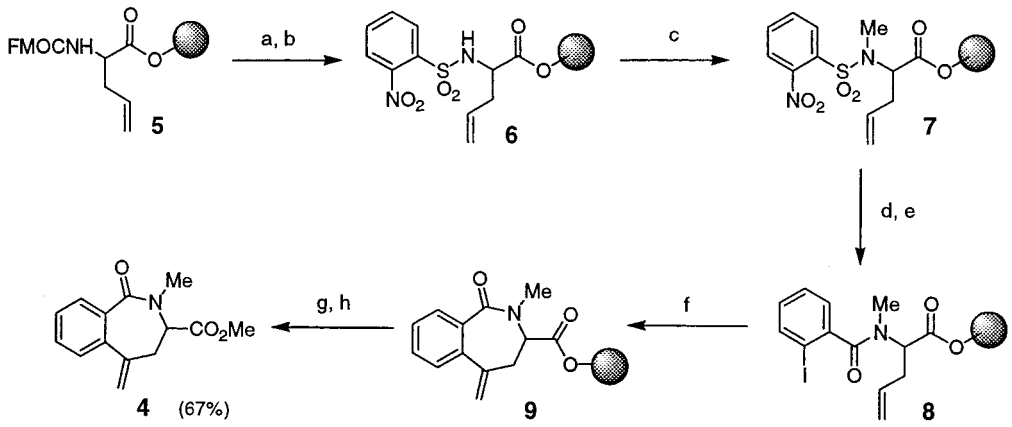


[a] Reagents and conditions: (a) 2-iodobenzoyl chloride, Et_3N, CH_2Cl_2; (b) NaH, MeI, THF; (c) $Pd(OAc)_2$, PPh_3, Bu_4NCl, KOAc, DMF, 70 °C.

propargylglycine methyl ester (**14**) with 2-iodobenzoyl chloride provided benzamide **15**, which underwent smooth palladium-catalyzed alkyne arylation with iodobenzene to afford **16.** N-Methylation as before gave the desired cyclization precursor **17**. Intramolecular Heck cyclization, using sodium formate (2 eq) to reduce the intermediate vinyl palladium species, provided the desired bicyclic lactam **18**, although in only 34% yield. The major product **19** (65%) was derived from a reductive deiodination. Although modification of the cyclization conditions (portionwise addition of sodium formate) nearly eliminated the formation of **19**, a larger amount of polymeric material was formed and yields of **18** never exceeded 40%. Nonetheless, with some of the desired product **18** in hand and an understanding of a potential byproduct that could be obtained, this route was adapted to a solid-supported format.

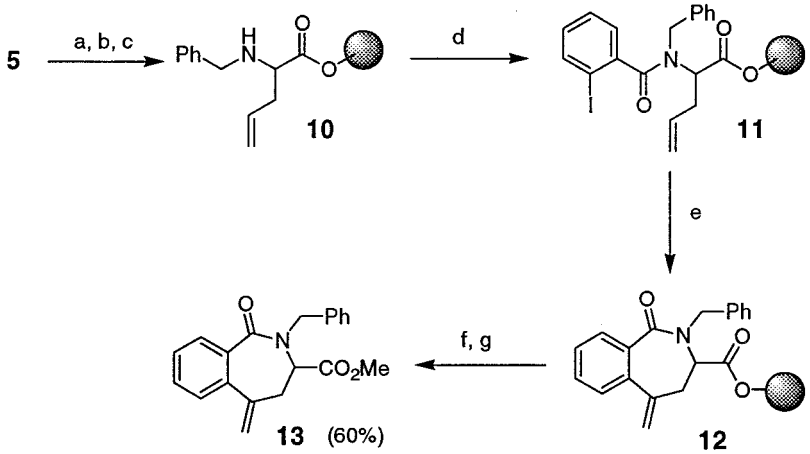
As shown in Scheme 6, Wang resin-linked FMOC-propargylglycine **20**[3] was converted to **21** which underwent N-methylation, deprotection, and acylation as before to afford **22**. Palladium-catalyzed alkyne arylation with iodobenzene provided the cyclization precursor **23**. We were gratified to find that treatment of resin **23** under conditions similar to those used in solution provided solely the desired bicyclic product **18** in 63% overall yield after cleavage. The olefin geometry was assigned based on the expected overall cis addition of palladium to the alkyne. No deiodinated material could be detected after esterification. The factors responsible for this selectivity are not clear. Concentration may play a critical role, as the solid-phase reactions were performed in IRORI microreactors, with effective concentrations approximately 5-fold less than in solution. Alternatively, it is

Scheme 3[a]



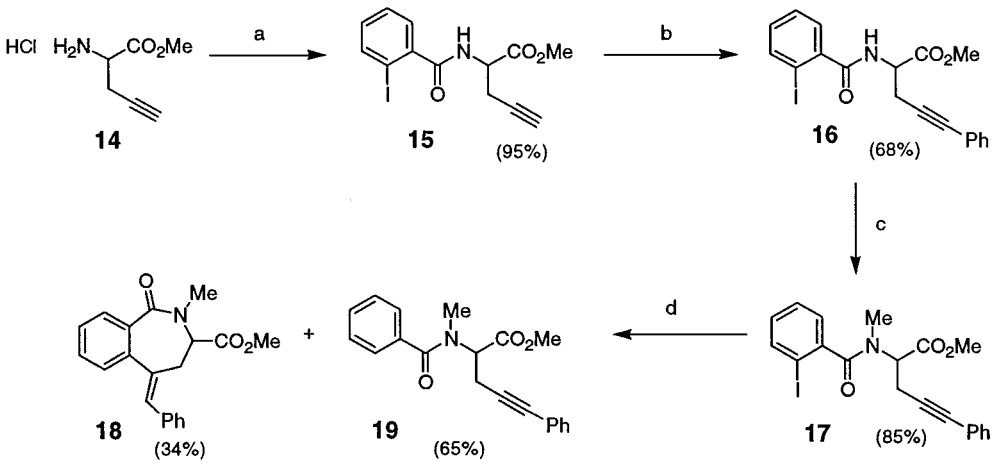
[a] Reagents and conditions: (a) piperidine, DMF; (b) 2-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2; (c) MTBD, MeI, DMF; (d) PhSH, K_2CO_3, DMF; (e) 2-iodobenzoyl chloride, Et_3N, CH_2Cl_2; (f) $Pd(OAc)_2$, PPh_3, Bu_4NCl, KOAc, DMF, 70 °C; (g) TFA/CH_2Cl_2 (1:1); (h) CH_2N_2.

Scheme 4[a]



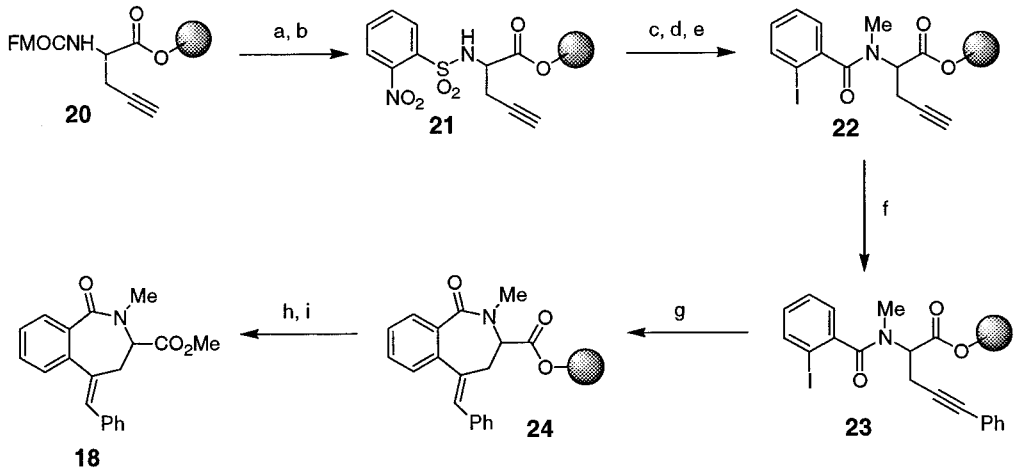
[a] Reagents and conditions: (a) piperidine, DMF; (b) benzaldehyde, $(MeO)_3CH$; (c) $NaBH(OAc)_3$, HOAc, CH_2Cl_2; (d) 2-iodobenzoyl chloride, Et_3N, CH_2Cl_2; (e) $Pd(OAc)_2$, PPh_3, Bu_4NCl,KOAc, DMF, 70 °C; (f) TFA/CH_2Cl_2 (1:1); (g) CH_2N_2.

Scheme 5[a]



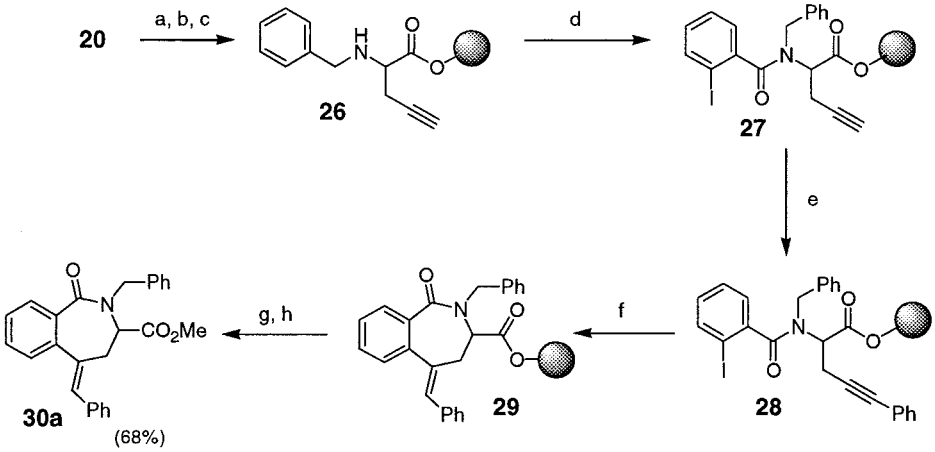
[a] Reagents and conditions: (a) 2-iodobenzoyl chloride, Et_3N, CH_2Cl_2; (b) $(PPh_3)_2PdCl_2$, CuI, PhI, Et_3N, CH_2Cl_2; (c) NaH, MeI, THF; (d) $Pd(OAc)_2$, PPh_3, Bu_4NCl, HCO_2Na, DMF, 70 °C.

Scheme 6[a]



[a] Reagents and conditions: (a) piperidine, DMF; (b) 2-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2; (c) MTBD, MeI, DMF; (d) PhSH, K_2CO_3, DMF; (e) 2-iodobenzoyl chloride, Et_3N, CH_2Cl_2; (f) $(PPh_3)_2PdCl_2$, CuI, PhI, Et_3N, CH_2Cl_2; (g) $Pd(OAc)_2$, PPh_3, Bu_4NCl, HCO_2Na, DMF, 70 °C; (h) TFA/CH_2Cl_2 (1:1); (i) CH_2N_2.

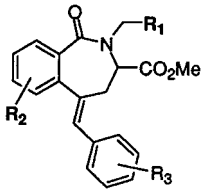
Scheme 7[a]



[a] Reagents and conditions: (a) piperidine, DMF; (b) benzaldehyde, $(MeO)_3CH$; (c) $NaBH(OAc)_3$, HOAc, CH_2Cl_2; (d) 2-iodobenzoyl chloride, Et_3N, CH_2Cl_2; (e) $(PPh_3)_2PdCl_2$, CuI, PhI, Et_3N, CH_2Cl_2; (f) $Pd(OAc)_2$, PPh_3, Bu_4NCl,KOAc, DMF, 70 °C; (g) TFA/CH_2Cl_2 (1:1); (h) CH_2N_2.

possible that some inorganic material from the previous alkyne arylation step remains trapped within the polymer matrix and enhances the subsequent Heck cyclization at the expense of the deiodination pathway in some way. Regardless, this route features a selective, sequential, inter- and intramolecular palladium-catalyzed arylation of both ends of the appended alkyne, resulting in efficient access to this new class of bicyclic amino acid derivatives.[11]

Table 1



entry	R_1	R_2	R_3	yield (%)
30a	Ph	H	H	39
30b	Ph	H	4-CONHBu	55
30c	Ph	H	3-CF_3	50
30d	Ph	7-Cl	H	69
30e	Ph	7,8-diOMe	H	47
30f	CH_2CH_2Ph	H	H	73

Incorporation of the reductive amination process for N-functionalization proceeded in analogous fashion as shown in Scheme 7. Resin-bound secondary amine **26** was obtained from **20** and underwent acylation and alkyne arylation as before to give the cyclization precursor **28**. Reductive cyclization afforded **30a** in good overall yield after TFA cleavage and esterfication.

The route depicted in Scheme 7 has been used to generate variously substituted benzazepines as shown in Table 1. Aromatic and aliphatic aldehydes are compatible in the reductive amination step, and a variety of aryl iodides could be employed in the alkyne arylation step. The bicyclic products are typically obtained in overall yields of approximately 40−70% for this multistep sequence. Yields for entries **30a,b,e** are for analytically pure compounds obtained after flash chromatography. An X-ray crystal structure determination of **30e** (see Figure 1, Supporting Information) confirmed the *E*-olefin assignment, and also revealed a boatlike conformation for the lactam ring which distorts the exocyclic benzylidene moiety from planarity. Yields for entries **30c,d,f** were obtained following minimal purification (filtration of the crude esters through a small silica gel cartridge), which resulted in HPLC purities of 93, 71, and 77%, respectively.

In conclusion, a novel solid-phase application of a 7-exo Heck cyclization has been developed for the construction of substituted benzazepines. This new class of bicyclic amino acid scaffold can be efficiently functionalized at various sites via Fukuyama amine synthesis, reductive amination, and alkyne arylation protocols. Library generation efforts are ongoing and will be reported in due course.

Acknowledgment. The authors thank Dr. Ron Rubin for the X-ray crystal structure determination.

Supporting Information Available. Experimental and spectroscopic data for all compounds and X-ray crystallographic data for **30e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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