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Combinatorial Chemistry. Use of an Intramolecular Ruthenium Catalyzed Olefin/Alkyne Metathesis Reaction in Tandem With a Diels-Alder Cycloaddition Reaction to Construct Functionalized Hexahydroisoindoles.

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Abstract. We show here the first example of a ruthenium catalyzed ene-yne metathesis reaction in tandem with a Diels-Alder cycloaddition reaction to efficiently form highly substituted hexahydroisoindole ring systems on Wang resm. This approach was used to prepare a 4200 membered combinatorial library. © 1998 Elsevier Science Ltd. All rights reserved.

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Recently, there has been considerable interest in expanding the scope of polymer-supported chemistry for the preparation of increasingly more complex organic molecules.¹ This powerful technique has been used to rapidly produce large numbers of potentially biologically relevant compounds both in a combinatorial fashion and by multiple simultaneous syntheses.² We were interested in efficiently synthesizing a large number of novel compounds in a combinatorial fashion on solid support based on a structurally well-defined



template. This led us to explore concise methods of synthesizing polycyclic ring systems, in particular, functionalized hexahydroisoindoline rings. Our design is illustrated in a retrosynthetic fashion in Scheme 1. We chose to construct the 6-membered ring of the isoindoline nucleus 1 by a Diels-Alder cycloaddition reaction. There is ample precedent that this powerful ring-forming reaction works on solid phase.³ Since the

Diels-Alder reaction could potentially produce mixtures of diastereomeric products, we elected to perform this reaction last, thereby maximizing our potential to maintain a clean reaction profile. We chose to immobilize the diene on resin which would allow us to take advantage of the large range of commercially available dienophiles to introduce diversity in the library. We envisioned forming diene 2 by an intramolecular ruthenium catalyzed metathesis reaction of the ene-yne 3.⁴ At the outset of this work, the level of substitution that could be tolerated on the ene-yne moiety was not well established and the ruthenium catalyzed ene-yne metathesis reaction had not been demonstrated on solid phase.⁵ Ene-yne 3 should be available from an allyl amine, a carboxylic acid, and an appropriately functionalized alkyne.



(a) EDC, HOBt·H₂O, Et₃N, DMF, RT, 18h (**6a**: 85%; **6b**: 82%); (b) t - NaH, DMF, RT, 30 min, ii - $R^2CH_2C\equiv CCH_2OMs$, RT, 5h (**7a**: 71%; **7b**: 48% {recovered **6b**; 41%}); (c) RuCl₂(=CHPh)(PCy₃)₂ 3 mol%, benzene, reflux, 18h (**8a**: 90%; **8b**: 96%); (d) maleimide, toluene, reflux, 18h (30% {recovered **8b**: 52%}).

The feasibility of the chemistry was examined in solution starting with 4-benzyloxybenzoic acid 4, which was chosen to mimic the linker found on Wang resin. Compounds **7a** and **7b** were prepared as shown in Scheme 2 using the known amines **5a** and **5b**⁶ and the mesylates of the corresponding alkynols. Treatment of **7a** and **7b** with 3 mol% of RuCl₂(=CHPh)(PCy₃)₂⁷ under optimized conditions in degased, refluxing benzene, gave **8a** and **8b** in 90% and 89% isolated yields, respectively. These results confirmed that substitution at the terminus of the alkyne was not deleterious to the methathesis reaction and further established that sterically demanding substitution at the allylic position of the alkene was well tolerated (**7b** \rightarrow **8b**). Next, we examined the Diels-Alder cycloaddition reaction to form the hexahydroisoindole ring system. The reaction conditions had to be compatible with our choice of acid labile solid support and therefore, we started with the thermally catalyzed reaction in refluxing toluene. Under these conditions diene **8b** was condensed with maleimide to give the cycloadduct *rac*-**9** in good yield as a single diastereomer. The results from ¹H NMR n.O.e. experiments are consistent with the relative stereochemistry shown in Scheme 2. The solution phase work showed that the reactions were either high yielding, or proceeded with moderate conversion and a very clean reaction profile, *i.e.* they gave only desired product and unreacted starting materials. We anticipated that the latter reactions could be driven to completion on solid phase by the use of excess reagents and/or multiple reaction cycles.

The solid phase chemistry was initiated by reacting the sodium anion of the allyl 4-hydroxybenzoate with chloro-Wang resin⁸ in DMF to give **10**. All of the reactions were characterized on solid phase using magic angle spinning ¹H NMR (MAS NMR).⁹ The corresponding reaction of allyl 4-hydroxybenzoate with Wang



(a) $(Ph_3P)_4Pd$, 10% PhNHCH₃ in 1:1 DMSO/DMF, 55 °C, 18h; (b) $H_2NCH(R^1)CH=CH_2$, EDC, HOBt· H_2O , Et₃N, DMF, RT, 18h; (c) i - t-BuOLi, THF, RT, 1.5h, ii - R²CH₂C=CCH₂OMs, DMSO, 5h; (d) RuCl₂(=CHPh)(PCy₃)₂ 5 mol%, benzene, 75 °C, 18h; (e) maleimide, toluene, 105 °C, 18h.

resin under Mitsunobu reaction conditions¹⁰ was less successful, giving resin-bound material that was always contaminated with 5-10% resin-bound diethyl hydrazinedicarboxylate.¹¹ The allyl ester of **10** was removed using 20 mol% Pd(PPh₃)₄ in the presence of N-methyl aniline to give 11.¹² We initially loaded methyl 4hydroxybenzoate onto the resin but were unable to successfully hydrolyze the methyl ester under a variety of basic and nucleophilic conditions. Reaction of 11 with allyl amine or 3-amino-4-methyl-1-pentene^{6a} proceeded smoothly to give 12a or 12b as shown. Compounds 12a or 12b were treated with a 10-fold excess of lithium tert-butoxide to give the corresponding lithium amide. After draining away the excess lithium tert-butoxide, the resin-bound anion was reacted with a five-fold excess of 2-butynyl methanesulfonate in DMSO to give the desired products 13a and 13b, together with some unreacted starting material. This mixture was subjected to one more cycle of lithium tert-butoxide and 2-butynyl methanesulfonate to convert the remaining 12a or 12b to the corresponding products 13a and 13b. Other soluble strong bases, such as lithium, sodium, or potassium bis(trimethylsilyl)amide could not be used, as 13a and 13b were not stable to these conditions, and therefore the reaction could not be driven to completion through the use of multiple reaction cycles. Treatment of 13a and 13b with 5 mol% of RuCl₂(=CHPh)(PCy₃)₂ in degased, gently refluxing benzene for 18h gave 14a and 14b. These results demonstrate that Wang resin and our choice of R^2 and R^3 do not have a detrimental effect on the efficiency of the metathesis reaction. Treatment of 14a and 14b with maleimide in refluxing toluene gave the resin-bound cycloadducts 15a and 15b as single diastereomers. The relative stereochemistry of 15a and 15b is as depicted in Scheme 3 and is consistent with nuclear Overhauser effects in the ¹H NMR spectrum of the material cleaved from resin. These results are similar to those obtained from the corresponding solution phase reaction, indicating that the resin did not influence the stereochemical outcome of the Diels-Alder cycloaddition reaction.

This reaction sequence was used in a "split and mix" fashion to prepare a 10 x 4 x 5 x 16 membered isoindoline combinatorial library.¹³ We selected 24 beads at random from each of the final 16 sublibraries and subjected them individually to 5% H₂O in TFA followed by analyzing the resin-cleaved material by LC-MS. This revealed that, for 14 out of the 16 sublibraries, \geq 70% of the beads examined contained identifiable material that was \geq 70% pure by LC-MS analysis. Additionally, the LC-MS analyses of beads from 7 of the sublibraries revealed that there were 2 components present, comprising \geq 70% of the material, with identical masses. This is consistent with the formation of diastereomeric Diels-Alders cycloaddition adducts. The LC-MS analysis of the

beads from the remaining 2 out of the 16 sublibraries (those derived from the attempted Diels-Alder cycloaddition reactions with *p*-toluenesulfonyl cyanide and crotononitrile) gave no identifiable products.

In conclusion, we have demonstrated for the first time on solid support, an intra-molecular rutheniummediated ene-yne metathesis reaction to form a diene which was subsequently used in a Diels-Alder cycloadditon reaction. This sequence was used to prepared an isoindoline combinatorial library theoretically containing 4200 unique members. The chemistry worked well for the range of substrates that we chose, with transformations that were high yielding or amenable to repetitive cycling under the reaction conditions to drive the reaction to completion. The reaction profiles were clean, minimizing the production of resin-bound impurities and the synthetic sequence was relatively short, minimizing the number of chemical steps on solid support while maximizing the level of introduced diversity. Studies to exploit this sequence to give other functionalized ring systems are underway and will be reported in the future.

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References and Notes

- 1. Marx, M.A.; Grillot, A. -L.; Louer, C.T.; Beaver, K.A.; Bartlett, P.A. J. Am. Chem. Soc. 1997, 119, 6135-6167.
- (a) An, H.; Haly, B.D.; Cook, P.D. J. Med. Chem. 1998, 41, 706-716. (b) Ostrem, J.A.; Al-Obeidi, F.A.; Safar, P.; Safarova, A.; Stringer, S.K.; Patek, M.; Cross, M.T.; Spoonamore, J.; LoCascio, J.C.; Kasireddy, P.; Thorpe, D.; Sepetov, N.; Lebl, M.; Wildgoose, P.; Strop, P. Biochemistry 1998, 37, 1053-1059. (c) Nicolaou, K. C.; Vourloumis, D.; Li, T.; Pastor, J.; Winssinger, N.; He, Y.; Ninkovic, S.; Sarabia, F.; Vallberg, H.; Roschangar, F.; King, N.P.; Finlay, M.R.V.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. Angew. Chem. Int. Ed. Engl. 1997, 36, 2097-2103.
- (a) Yedidia, V.; Leznoff, C.C. Can J. Chem. 1980, 58, 1144-1150. (b) Schlessinger, R.H.; Bergstrom, C.P. Tetrahedron Lett. 1996, 37, 2133-2136.
- (a) Kinoshita, A.; Mori, M. Synlett 1994, 1020-1022. (b) Kinoshita, A.; Mori, M. J. Org. Chem. 1996, 61, 8356-8357. (c) Kim, S.-H.; Zuercher, W.J.; Bowden, N.B.; Grubbs, R.H. J. Org. Chem. 1996, 61, 1073-1081.
- 5. After the completion of this work, an example of an intermolecular ruthenium-catalyzed ene-yne cross metathesis on Merrifield resin was published. Schurer, S.C.; Blechert, S. *Synlett* **1998**, *2*, 166-168.
- 6. 3-Amino-4-methylpent-1-ene (5b): Tamao, K.; Nakagawa, Y.; Ito, Y. J. Org. Chem. 1990, 55, 3438-3439.
- 7. Kim, S.-H.; Bowden, N.; Grubbs, R.H. J. Am. Chem. Soc. 1994, 116, 10801-10802.
- Chloro-Wang resin was prepared from commercially available Wang resin (Polymer Labs; Lot No. Wang008; 250-300 μM mesh; 1.7 meq/g loading) according to Raju, B.; Kogan, T.P. *Tetrahedron Lett.* **1997**, *38*, 4965-4968
- 9. The identity and purity of the products were further established by cleaving an aliquot of the resin-bound material with 5% H₂O in TFA. In all cases, the desired resin-cleaved material was identified by mass spectroscopy and ¹H NMR analysis. The material was also >98% pure by reverse phase HPLC analysis.
- 10. Hamper, B.C.; Dukesherer, D.R.; South, M.S. Tetrahedron Lett. 1996, 37, 3671-3674.
- 11. Apparently, the diethyl hydrazinedicarboxylate by-product of the Mitsunobu reaction effectively competed with the phenol as an alkylating agent for the resin. The side reaction could be suppressed by using a large excess of the allyl 4-hydroxybenzoate.
- 12. Seitz, O.; Kunz, H. Angew. Chem. 1995, 107, 901-904.
- 13. The R¹ component consisted of aryl or arylalkyl groups optionally substituted with halogen, alkyl and alkoxy groups. The R² component consisted of hydrogen, alkyl or arylalkyl groups. The R³ component consisted of hydrogen or alkyl groups. The dienophiles included cyclic, *cis* and *trans* disubstituted olefins containing at least one electron withdrawing group and alkynes containing at least one electron withdrawing group.