Tetrahedron Letters,Vol.24,No.20,pp 2051-2054,1983 0040-4039/83/202051-04$03.00/0
Printed in Great Britain

Efficient Coupling Reactions of β-Amino and β-Acetamido Radicals with Electron Deficient Alkenes - Aza-Carbofunctionalization of Olefins - A Promising New Tool for Alkaloid Synthesis.

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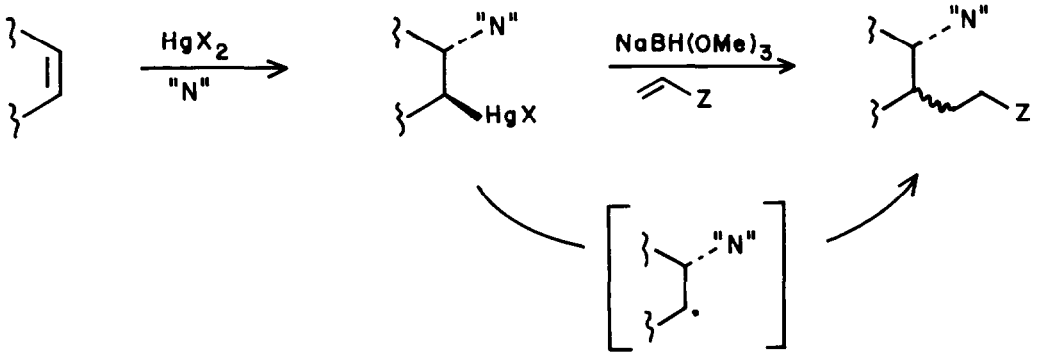
Summary: The coupling reactions of β-amino and β-acetamido radicals prepared by reduction of organomercurials have been examined as a potentially new approach to alkaloid construction.

Giese and co-workers have reported over the past several years in a number of articles that radicals formed on reduction of organomercurials can be trapped with electron deficient olefins to produce coupled products.[1] Since this process does represent a tremendously versatile new method for producing vicinally functionalized molecular systems, we felt that additional studies were warranted. We have in fact shown recently that the radicals formed from the β-hydroxymercurials couple efficiently with activated olefins to deliver products that can be cyclized to δ-lactones. This "3+3" joining strategy for the production of such systems was used to assemble the naturally occurring antibiotic malyngolide.[2]

As the second stage of our studies, we turned our attention to the question of whether the organomercurial generated from the azido, nitro, acetamido or aminomercuration of an olefin could be used in this coupling scheme, for we envisioned that the products of this overall aza-carbofunctionalization process could serve as important building blocks for alkaloid synthesis.



The mercurials listed in the accompanying table were prepared by known literature procedures. Thus, the method of Bachman and Whitehouse was used to synthesize β-nitromercurial 1.[3] The azidomercuration product 2 was prepared from sodium azide and mercuric chloride in analogy to the procedure of Sokolov and Reutov.[4] Reaction of an alkene with mercuric nitrate and acetonitrile delivered the generally crystalline acetamidomercurials after ligand exchange with sodium chloride as reported by Beger and Vogel.[5]

The coupling reactions of these mercurials with acrylonitrile and methyl acrylate were examined under a standard set of conditions developed for each trapping agent. For reactions in which acrylonitrile was used, the mercurial (2.0 mmol) was dissolved in methylene chloride (30 mL) and acrylonitrile (2.0 mL, 30 mmol) was added. The stirred mixture was cooled to 0°C and 12 mL of a 0.5 M solution of sodium trimethoxyborohydride in THF was added by syringe pump over 30 min. After an additional 1 h at room temperature, the reaction was quenched with water and extracted with ethyl ether. The crude product obtained upon concentration was chromatographed on silica gel to afford the coupled product. With methyl acrylate as the trapping agent, the coupling reaction was performed by adding 4 mL of an 0.5 M solution of sodium trimethoxyborohydride in THF dropwise over a 30 min period to a solution of ~ 0.6 mmol of the mercurial in 10 mL of methylene chloride and 0.6 mL of methyl acrylate cooled to -7°C. The reaction was quenched with water and extracted with ethyl ether. The crude isolated product was chromatographed on silica gel and then analyzed by vpc.

As is readily apparent from the table, both the nitro- and azidomercurials fail to give coupling products under these conditions. Such mercurials are well known to regenerate the olefin from which they were prepared on exposure to relatively weak nucleophiles, thus explaining the absence of any detectable amounts of coupled product.[3]

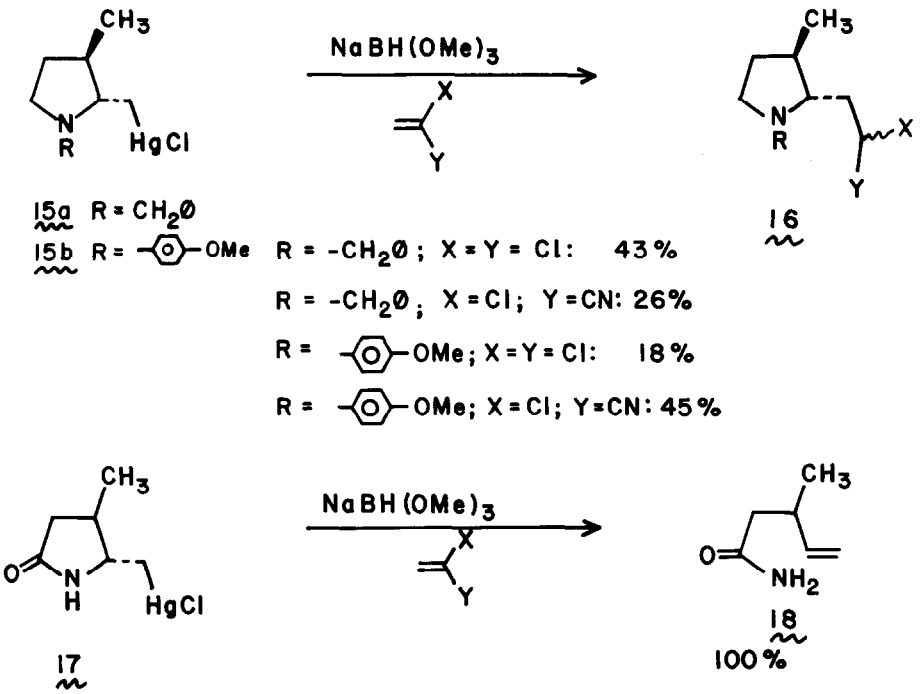
With the amino- and acetamidomercuration products, however, coupling did proceed in modest to good yield with acrylonitrile as the trapping agent. The coupling products of 1-chloromercuri-2-acetamidocyclohexane with acrylonitrile were separable by gravity chromatography. ^{1}H NMR analysis revealed that the trans-product was the major isomer (60:40).[6] The acetamidomercurial prepared from cis-2-butene likewise suffered considerable erosion of its stereochemical purity in the coupling process, for a 68:32 mixture of the threo/erythro products was formed. These two examples do clearly point out one fairly obvious shortcoming of such radical-based coupling procedures.

With methyl acrylate, it was found that the product of simple reduction without trapping generally predominated. Hence, acrylonitrile is clearly the reagent of choice when the appendage of three-carbon atoms is desired.

In order to apply the aminomercuration/reductive coupling process to five-membered ring alkaloids, such as the pyrrolizidines, it is essential that one be able to couple the β-amino-radicals with a two carbon unit. The acetamidomercurial 6 was thus reduced with sodium trimethoxyborohydride in the presence of 1,1-dichloroethylene.[7] A 77% yield of the desired coupled product was generated. With the mercurials 15a, 15b and 17, formed from intramolecular amino- or amido-mercuration of the corresponding olefinic starting materials,[8] coupling reactions were examined using both 1,1-dichloroethylene and α-chloroacrylonitrile as the trapping agents. We assume that the stereochemistry of the mercurials are as shown, for concerted anti attack of amine on mercurinium ion should occur through that transition state which minimizes steric interactions.[9] Only in the case of 17 was no coupled product generated, for retro-amidomercuration took place instead to return the starting olefin. Mercurials 15a and 15b gave rise to reasonable amounts of 16 when chloroacrylonitrile was employed as the trapping agent.[10]

The method of aza-carbofunctionalization described herein should find use in the synthesis of a variety of alkaloid systems. Reports concerning this situation will be forthcoming.

Acknowledgements. We are indebted to the National Institutes of Health (AI-16138) for support of these investigations. We thank Dr. David Vanderah for carrying out some initial experiments in this area.



References and Notes

1. (a) B. Giese, H. Horler and W. Zwick, Tetrahedron Lett., 23, 931 (1982); (b) B. Giese and J. Meixner, Chem. Ber., 114, 2138 (1981). Giese has also investigated several examples of the aminomercuration/coupling process. We thank him for making this information available to us. See, K. Heuck, Dissertation, Darmstadt (1980).

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5. V. J. Beger and D. Vogel, J. Prakt. Chem., 311, 737 (1969); H. C. Brown and J. T. Kurek, J. Am. Chem. Soc., 91, 5647 (1969).

6. B. Giese and K. Heuck, Chem. Ber., 112, 3759 (1979).

7. Giese has made an extensive study of the trapping of the cyclohexyl radical by a variety of activated olefins: B. Giese and J. Meister, Chem. Ber., 110, 2588 (1977) and reference 1b.

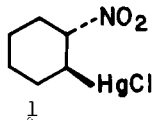
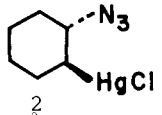
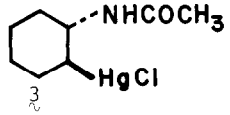
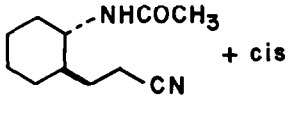
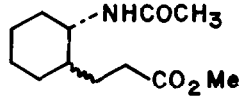
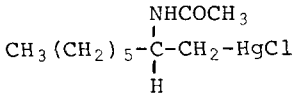
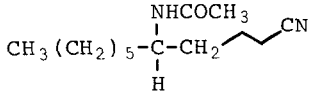
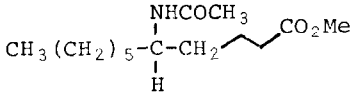
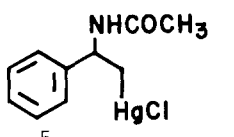
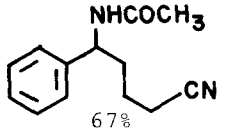
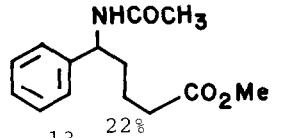
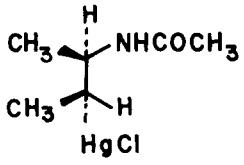
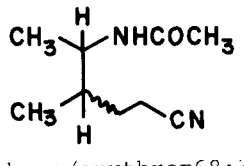
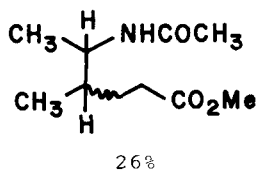
8. Such intramolecular azamercuration reactions do have ample precedent. See, for example: J. J. Périé, J. P. Laval, J. Roussel and A. Lattes, Tetrahedron, 28, 675 (1972).

9. When the intramolecular aminomercuration reaction was carried out with the nitrogen atom bearing a phenyl group, a 60:40 mixture of isomers 15c was generated (R=Ph). On borohydride reduction, the major isomer was found to exhibit methyl group doublets at δ = 1.05 and 1.22

ppm in its 300 MHz ^1H NMR. The minor isomer possessed two doublets at δ = 1.05 and 1.09 ppm. The alkyl group shielding effect leads us to assign trans stereochemistry to the major isomer. Since the chemical shift data for the reduction products derived from 15a and 15b are similar to that found for the major isomer derived from 15c, we assume that 15a and 15b possess the trans stereochemistry as depicted above.

10. For related work see: S. Danishefsky, E. Taniyama and R. R. Webb II, Tetrahedron Lett., 24, 11 (1983); S. Danishefsky and E. Taniyama, Ibid., 24, 15 (1983).

Table. Aza-Carbofunctionalization of Olefins

Mercurial	Coupling Product with acrylonitrile and Yield (%)	Coupling Product with methyl acrylate and Yield (%)
 1		
 2		
 3	 ratio = 60:40; 78% 7	 15% 11
 4	 67% 8	 40% 12
 5	 67% 9	 22% 13
 6	 threo/erythro=68:32, 74% 10	 26% 14

(Received in USA 14 December 1982)