Rearrangement in the Palladium-Catalyzed Cyclization of α-Substituted *N*-Acryloyl-*o*-bromoanilines

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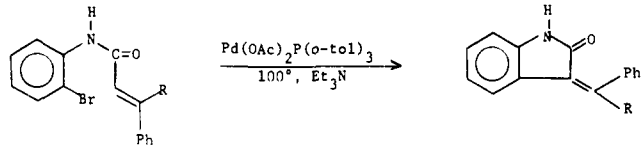
Abstract: *N*-Cinnamoyl- and *N*-(β-methylcinnamoyl)-*o*-bromoanilines undergo cyclization to oxindole derivatives when heated with catalytic amounts of palladium acetate and tri-*o*-tolylphosphine in the presence of triethylamine. *N*-(α-Methacryloyl)- and *N*-α-phenylacryloyl-*o*-bromoaniline, on the other hand, cyclize under the same conditions, to rearranged, 4-substituted 2-quinolones. A mechanism is proposed which may also be applicable to rearrangements observed with some coenzyme B_{12a} derivatives.

The wide applicability of the palladium catalyzed arylation of olefins to form open chain products has been well documented.[1] We have recently begun to look for applications of the reaction in the synthesis of cyclic compounds. We have reported upon the formation of 2-quinolone derivatives from the reaction of *o*-iodoaniline with various unsaturated carboxylic acids and their derivatives.[2] We now have investigated the palladium-catalyzed (intramolecular) cyclization of various *N*-acryloyl-*o*-bromoaniline derivatives and find very significant differences from the above intermolecular reaction.[2] This reaction has been studied independently with another reactant by Mori and co-workers.[3]

Results and Discussion

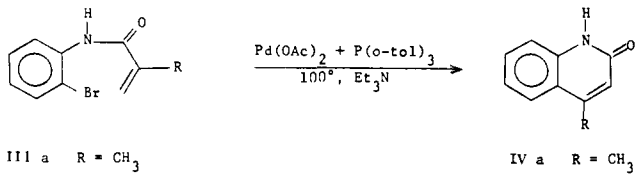
Cyclization of both *N*-cinnamoyl- and *N*-(β-methylcinnamoyl)-*o*-bromoaniline at 100 °C with 1 mol % palladium acetate and 4 mol % tri-*o*-tolylphosphine led to the formation of oxindole derivatives only: 3-benzylideneoxindole (58%) (IIa) and 3-(α-methylbenzylidene)oxindole (21%) (IIb), respectively. The only other product isolated was 20% unreacted bromoamide in the second case. The five-membered ring is clearly preferred over the possible six-membered 2-quinolone which was obtained as the sole cyclized product in the intermolecular reaction studied previously.[2] This result is consistent with the findings of Mori.[3]



I a R = H
b R = CH_3

II a R = H
b R = CH_3

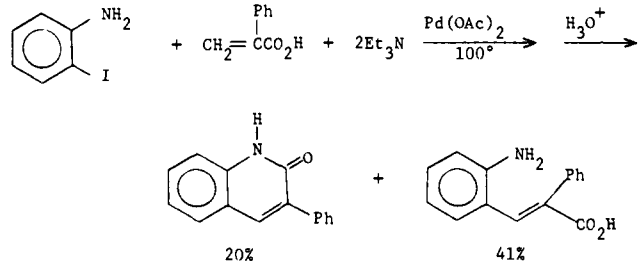
We attempted to favor the ring closure to the six-membered quinolone products in the reaction by cyclizing α-substituted *N*-acryloyl-*o*-bromoanilines. It was reasoned that the aryl group would prefer to add to the terminal methylene carbon rather than the tertiary carbon, as observed in reactions when rings are not produced.[1] 2-Quinolone derivatives were formed but, surprisingly, their structures were not the expected ones. Two compounds were tested: one with an α-methyl group (IIIa) and the other with an α-phenyl group (IIIb). The products in both cases were the 4-substituted 2-quinolones, IVa and IVb, isolated in 43% and 36% yields, respectively, rather than the expected 3-substituted derivatives.



III a R = CH_3
b R = Ph

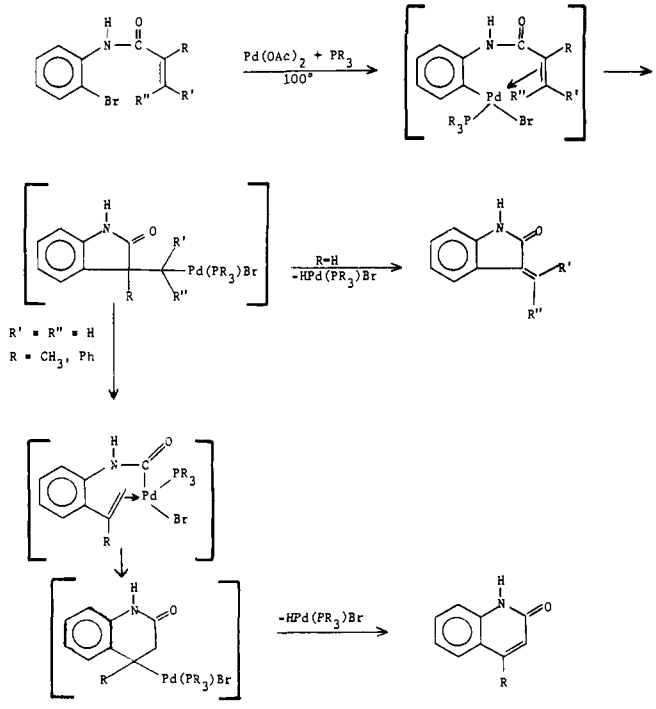
IV a R = CH_3
b R = Ph

The identity of the products from the reactions was established by comparison with authentic samples. No rearrangement was observed in the palladium-catalyzed cyclization reaction of *o*-iodoaniline with methyl methacrylate carried out previously[2] or with 2-phenylacrylic acid carried out in this study. The cyclization of the α-phenyl derivative gave 20% of 3-phenyl-2-quinolone and 41% of (presumably *E*) 2-phenyl-3-*o*-aminophenylpropenoic acid.



20% 41%

The rearrangement observed can be rationalized on the basis of an initial ring closure of the organopalladium intermediate to a five-membered ring product containing a 3-palladomethyl group. In these complexes there is no β hydrogen to be eliminated with the palladium as there is when the α carbon is un-



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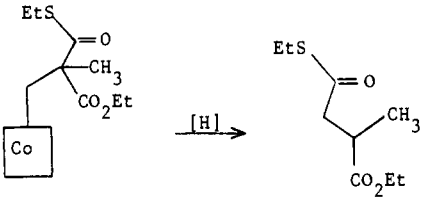
substituted. Because the usual decomposition reaction is not possible, elimination of the aminocarbonyl group with the palladium appears to occur and this is followed by a reverse readdition of the aminocarbonylpalladium group. The last adduct now can eliminate a hydridopalladium group irreversibly to give the observed, rearranged, 4-substituted 2-quinolone.

An attempt to cyclize *N*-(α-methylcinnamoyl)-*o*-bromoaniline under our usual conditions did not yield any identifiable product other than starting material. Presumably, the double bond is so substituted that it cannot coordinate effectively with the palladium in this example.

The palladium-catalyzed rearrangement observed in this study is probably closely related to the rearrangement of a thioester derivative of B_{12a} observed by Eggerer.[4] Recent results of a study of this reaction in deuterated ethanol are consistent with our mechanism with a final deuteration of the organocobalt intermediate by the solvent.[5] Probably these



rearrangements will prove to be general for transition metal alkyls which cannot undergo the usual β-hydrogen elimination.

Experimental Section

Table I, containing the NMR spectra and molecular weights determined from the products prepared, will appear only in the microfilm edition of the journal. (See note on supplementary material at the end of this paper.)

Reagents. Triethylamine (Aldrich), bromobenzene (Fischer Scientific), and acetonitrile (Baker) were stored over Davison 4A molecular sieves before use. Methacrylic acid, 2-bromoaniline, and cinnamoyl chloride were used as received from the Aldrich Chemical Co. 1-Bromostyrene,[6] 3-phenyl-2-butenoic acid,[7] tri-*o*-tolylphosphine,[8] and palladium acetate[9] were prepared by published procedures. Tri-*p*-tolylphosphine was made from *p*-tolylmagnesium bromide and phosphorus trichloride.

***N*-Cinnamoyl-*o*-bromoaniline.** A mixture of 16 g (0.1 mol) of cinnamoyl chloride, 17.5 g (0.1 mol) of *o*-bromoaniline, and 10 g (0.1 mol) of triethylamine was allowed to stand for 2 h. Water was then added and the product was extracted with three portions of ether. The ether layer was washed with dilute aqueous hydrochloric acid and dried with anhydrous magnesium sulfate. Evaporation of the solvent and crystallization of the solid residue from chloroform–heptane gave 14.9 g (50%) of the amide, mp 144–145 °C.

3-Benzylidene-2-oxindole. A solution of 10 mmol of *N*-cinnamoyl-*o*-bromoaniline, 0.10 mmol of palladium acetate, 0.40 mmol of tri-*p*-tolylphosphine, 4 mL of acetonitrile, and 2 mL of triethylamine was heated under nitrogen at 100 °C in a heavy-walled capped Pyrex tube for 18 h. The cooled, partially solid reaction mixture was rinsed into a round-bottomed flask with methylene chloride and the volatile material was removed under aspirator vacuum at room temperature. About 200 mL of ether and 50 mL of water were added to the residue and, after shaking to dissolve the solids, the layers were separated. The ether extract was dried with magnesium sulfate and the solvent was removed under aspirator vacuum. The residue was recrystallized from chloroform–heptane to give 1.28 g (58%) of 3-benzylidene-2-oxindole, mp 175–176 °C (reported 175–176 °C[10]).

***N*-(α-Methylcinnamoyl)-*o*-bromoaniline.** This material was prepared by the method of Brewster.[11] To a solution of 10 g (0.06 mol) of 3-phenyl-2-butenoic acid[7] and 20 mL of pyridine was added 4 mL (0.033 mol) of benzenesulfonyl chloride with cooling in an ice bath. After the mixture had cooled to room temperature, 5.3 g (0.03 mol) of *o*-bromoaniline was added. After stirring for 15 min, the mixture was kept in a freezer overnight. The reaction mixture was then diluted with aqueous sodium hydroxide and ether. The ether phase was separated, dried, and concentrated. Recrystallization of the residue from chloroform–heptane gave 8.5 g (87%) of the amide, mp 96–98 °C.

3-(α-Methylbenzylidene)-2-oxindol. A solution of 10 mmol of *N*-(β-methylcinnamoyl)-*o*-bromoaniline, 0.10 mmol of palladium acetate, 0.40 mmol of tri-*p*-tolylphosphine, 4 mL of acetonitrile and 2 mL of triethylamine was heated under nitrogen at 100 °C in a heavy-walled capped Pyrex tube for 29 h. After cooling, water and ether were added. The ether phase was separated, dried with magnesium sulfate, and concentrated. The residue was chromatographed on silica gel. Chloroform eluted the product. Recrystallization from chloroform–heptane gave 0.52 g (22%) of the oxindole, mp 194–195 °C (reported 193–194 °C[12]). There was also recovered from the chromatography 20% of the starting bromide.

***N*-(α-Methacryloyl)-*o*-bromoaniline.** This amide was also prepared by the Brewster method.[11] To a mixture of 6.8 g (0.1 mol) of methacrylic acid in 20 mL of pyridine was added 6.4 mL (0.05 mol) of benzenesulfonyl chloride. The mixture was cooled to room temperature and 8.6 g (0.05 mol) of *o*-bromoaniline was added. After stirring for 15 min, the mixture was left in the freezer overnight. Then aqueous sodium hydroxide and ether were added. The ether phase, after drying, was distilled under reduced pressure. The amide, bp 110–115 °C (0.8 mm), weighed 8.0 g (67%).

4-Methyl-2-quinolone. A mixture of 10 mmol of *N*-(α-methacryloyl)-*o*-bromoaniline, 0.10 mmol of palladium acetate, 0.40 mmol of tri-*o*-tolylphosphine, 4 mL of acetonitrile, and 2 mL of triethylamine was heated under nitrogen for 15.5 h at 10 °C. Isolation of the product as in the 3-benzylidene-2-oxindole preparation above and recrystallization from acetone gave 0.69 g (43%) of 4-methyl-2-quinolone, mp 224–225 °C (reported 223.7 °C[13]).

α-Phenylacrylic Acid. The Grignard reagent was prepared from 45 g (0.245 mol) of 1-bromostyrene[6] and 4.0 g of magnesium in 50 mL of dry THF under nitrogen. A few drops of ethylene bromide were used to initiate the reaction. The mixture was heated at reflux temperature for 3 h and poured onto an excess of powdered dry ice. The product was taken up in ether, the extract was washed with water, and the product was removed by extraction with aqueous sodium bicarbonate. Acidification of the bicarbonate extract gave the solid acid. After filtration and air drying, there was obtained 21 g (57%) of the acid, mp 106–107 °C (reported 106–107 °C[14]).

***N*-(α-Phenylacryloyl)-*o*-bromoaniline.** This amide was prepared by the method of Brewster[11] as in the *N*-(α-methacryloyl)-*o*-bromoaniline preparation above. The product, bp 205–207 °C (1 mm), was obtained in 60% yield.

4-Phenyl-2-quinolone. The cyclization of 10 mmol of *N*-(α-phenylacryloyl)-*o*-bromoaniline was carried out as described for the *N*-(α-methacryloyl) compound. After 19.5 h, the product was isolated as in the 3-benzylidene-2-oxindole preparation above. Recrystallization from acetone gave 0.82 g (36%) of the quinolone, mp 257–259 °C (reported 259 °C[15]). A mixture melting point of this product with an authentic sample[2] was not depressed. The 3-phenyl isomer described below melted 26 °C lower and had significant differences in its NMR spectrum. (See Table I in the microfilm edition for the NMR spectra.)

3-Phenyl-2-quinolone. A mixture of 2.19 g (10 mmol) of *o*-iodoaniline, 1.86 g (12.5 mmol) of α-phenylacrylic acid, 2.5 g (25 mmol) of triethylamine, and 0.10 mmol of palladium acetate was stirred at 100 °C under nitrogen for 24.5 h. After cooling, the reaction mixture was diluted with ether and water. The ether phase was separated, washed with aqueous base, dried, and concentrated under reduced pressure. The product was purified by recrystallization from acetone. This gave 0.46 g (20%) of the quinolone, mp 231–232 °C (reported 234–235 °C[16]). Acidification of the aqueous base extract gave a solid, which after separation by filtration and air drying was shown by NMR to be α-phenyl-*o*-aminocinnamic acid, 1.0 g (41%), mp 183–185 °C (reported 185–186 °C[17]).

***N*-(α-Methylcinnamoyl)-*o*-bromoaniline.** This amide was obtained from α-methylcinnamic acid[7] by the method of Brewster[11] as described above in the preparation of the β-methylcinnamoylamide. The amide, mp 53–55 °C, was obtained in 52% yield.

This amide failed to yield any isolatable cyclized product by the method employed for the β-methylcinnamoyl derivative above, after 114 h of reaction at 100 °C.

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Supplementary Material Available: Table I, a listing of NMR and mass spectroscopy data for the products prepared in this study (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) R. F. Heck, *Acc. Chem. Res.*, in press.
(2) N. A. Cortese, C. B. Ziegler, Jr., B. J. Hrnjez, and R. F. Heck, *J. Org. Chem.*, **43**, 2952 (1978).
(3) M. Mori, K. Chiba, and Y. Ban, *Tetrahedron Lett.*, 1037 (1977).
(4) H. Eggerer, F. R. Stadtman, P. Overath, and F. Lymen, *Biochem. Z.*, **331**, 1 (1960).
(5) A. I. Scott, J. Kang, D. Dalton, and S. K. Chung, *J. Am. Chem. Soc.*, **100**, 3603 (1978).
(6) R. P. Hanzlik and J. M. Hilbert, *J. Org. Chem.*, **43**, 612 (1978).
(7) B. A. Patel, C. A. Ziegler, N. A. Cortese, J. E. Plevyak, T. C. Zebovitz, M. Terpko, and R. F. Heck, *J. Org. Chem.*, **42**, 3903 (1977).
(8) C. B. Ziegler, Jr., and R. F. Heck, *J. Org. Chem.*, **43**, 2941 (1978).
(9) T. A. Stephenson, S. M. Morehousr, A. R. Powell, J. P. Heffler, and G. Wilkinson, *J. Chem. Soc.*, 3632 (1965).
(10) A. Wahl and P. Bagard, *Bull. Soc. Chim. Fr.*, **5**, 1036 (1909).
(11) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).
(12) A. Windaus, H. Jenson, and A. Schramme, *Chem. Ber.*, **57**, 1875 (1924).
(13) A. Reissert, *Chem. Ber.*, **24**, 255 (1891).
(14) A. Michalis, *Ann. Chim. (Paris)*, **315**, 79 (1901).
(15) R. Camps, *Arch. Pharm. (Weinheim, Ger.)*, **237**, 683 (1899).
(16) A. Bischler and M. Lang, *Chem. Ber.*, **28**, 242 (1895).
(17) R. Pschorr, *Chem. Ber.*, **28**, 498 (1896).

Lewis Acid Catalyzed Reactions of Methyl Propiolate with Unactivated Alkenes

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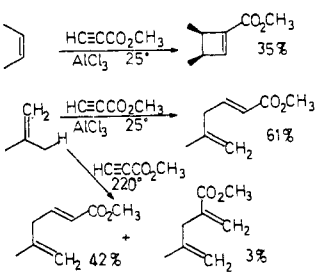
Abstract: Methyl propiolate undergoes Lewis acid catalyzed reactions with alkenes in high yield. Mono- and 1,2-disubstituted alkenes give mainly cyclobutenes. 1,1-Disubstituted, trisubstituted, and tetrasubstituted alkenes give only ene adducts. Use of ethylaluminum dichloride as catalyst allows the isolation of pure products from acid-sensitive alkenes. Functionalized alkenes containing nonbasic functional groups are suitable substrates. Alkenes containing more basic functional groups are suitable if 2 equiv of catalyst is used.

The use of carbon-carbon double bonds as activating groups for the formation of new carbon-carbon bonds under mild conditions is of considerable interest in organic synthesis. The ene reaction provides a potential solution to this problem. We have recently found that methyl propiolate[1] and 3-butyn-2-one[2] undergo Lewis acid catalyzed reactions at room temperature with a wide variety of alkenes giving either stereospecific [2 + 2] cycloadducts or ene adducts[3] depending on the substitution pattern of the alkene (Scheme I). These results contrast with the thermal reactions of methyl propiolate which proceed in low yield at 200–300 °C and give only ene adducts as mixtures of regioisomers.[4] The [2 + 2] cycloaddition has precedent in the cycloaddition of propiolate esters with enamines.[5] It has not been previously observed in nonphotochemical reactions of propiolates with unactivated alkenes.

In this paper we report significantly improved reaction conditions for the Lewis acid catalyzed reaction of propiolate esters with alkenes and describe our studies on the scope and limitations of this reaction, application to functionalized alkenes and studies directed toward elucidation of the mechanism of this reaction. The results of these studies are shown in Table I. The majority of these addition reactions were carried out with our initial conditions. Methyl propiolate is added to aluminum chloride in benzene. After the aluminum chloride has dissolved, the alkene is then added.[6] Although this procedure works well, isomerization of the alkene and addition of hydrogen chloride to the alkene or ene adduct often lead to byproducts. *We have recently found that ethylaluminum dichloride in either benzene or methylene chloride gives excellent yields of products uncontaminated with chlorine containing products or products resulting from isomerized alkene.* We believe that this dramatic improvement is due to the ability of ethylaluminum dichloride to act as a proton scavenger as well as a Lewis acid. Recent kinetic studies seem to indicate that the Lewis acid complexes preferentially with the product. *Therefore optimal yields are usually obtained with close to 1 equiv of ethylaluminum dichloride and reaction times of ca. 1 day.* In most of the cases in Table I, no attempt was made to optimize the amount of catalyst used. Yields greater than 80% can usually be obtained.

Scheme I



The formation of ene adducts is the exclusive reaction with alkenes containing at least one disubstituted carbon. 1,1-Disubstituted alkenes (cases 1–5), trisubstituted alkenes (cases 6–10), and tetrasubstituted alkenes (case 11) give ene adducts cleanly in good yield. Monosubstituted alkenes (cases 12 and 13) give mixtures of ene adduct and both of the possible cyclobutenes. Because of the ability of the trimethylsilyl group to stabilize positive charge at the β position, allyltrimethylsilane (**14**) gives only a single cyclobutene. This contrasts with the titanium tetrachloride catalyzed reactions of **14** with enones which give β-allylketones[7] but is similar to the cycloaddition of **14** with TCNE in nonpolar solvents which gives cyclobutanes.[8]

Cases 2 and 4 indicate that, with aluminum chloride as catalyst, isomerization of the alkene is sometimes a problem. This isomerization is probably catalyzed by hydrogen chloride. Use of ethylaluminum dichloride, which is both a milder catalyst and a hydrogen chloride scavenger, alleviates isomerization and allows the use of methylene chloride as solvent (cases 4, 31, 34, and 40). Under these conditions, optimal yields

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