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REACTIONS AND SYNTHESES WITH ORGANOMETALLIC COMPOUNDS. X. THE INTRAMOLECULAR CYCLIZATION USING ARYLPALLADIUM COMPLEXES FOR GENERATION OF NITROGEN-HETEROCYCLES

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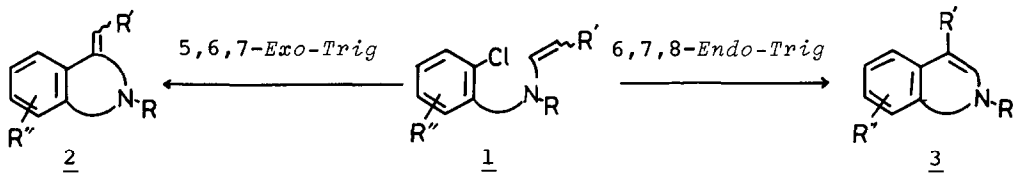
We have recently reported a new synthetic method of various heterocyclic compounds, such as indole, oxindole, quinoline, isoquinoline and benzazepine derivatives via arylnickel[1a, b] or arylpalladium complexes.[1c] On these cyclization reactions, there are two possibilities where the ring closure might occur in either *Exo*- or *Endo*-type of cyclization(See Chart 1).[2] If the ring closure of 1 would occur in an *Exo*-type, the product involving a smaller-membered ring indicated by formula(2) should be generated. On the other hand, an *Endo*-type of cyclization of 1 should provide a larger membered cycle represented by formula(3). In cases of our cyclization of 4 via arylnickel complexes(5),[1a] the oxindole derivatives(6 and 7) were obtained by *Exo*-cyclization, but the quinoline derivative(8) corresponding to an *Endo*-product was not detected.



2 1 3

Chart 1

In the meantime, Heck reported that reaction of o-iodoaniline(9) with dimethylmaleate with a catalytic amount of $Pd(OAc)_2$ in the presence of a base gave exclusively the quinoline derivative(10) in an excellent yield without generation of the oxindole(11).[3] These results are in a marked contrast with ours, although the catalysts were not same. Therefore, we reinvestigated the intramolecular cyclization of 13 by use of Pd^{II} as a catalyst. The compound(13) which was prepared from N-benzyl-o-bromoaniline(12) and maleic anhydride, was warmed with a catalytic amount of $Pd(OAc)_2$ and PPh_3 in the presence of $n\text{-}Bu_3N$ in acetonitrile at 70° for 6 hr to afford the expected oxindole(14) in 47.7% yield along with the starting material(13, 23.8%), but the quinoline derivative [8(R=CH_2Ph, R'=COOMe, R"=H)] was not detected at all. Similarly, the compound (15) gave the oxindole derivatives(16 and 17) in yields of 13% and 60%, respectively

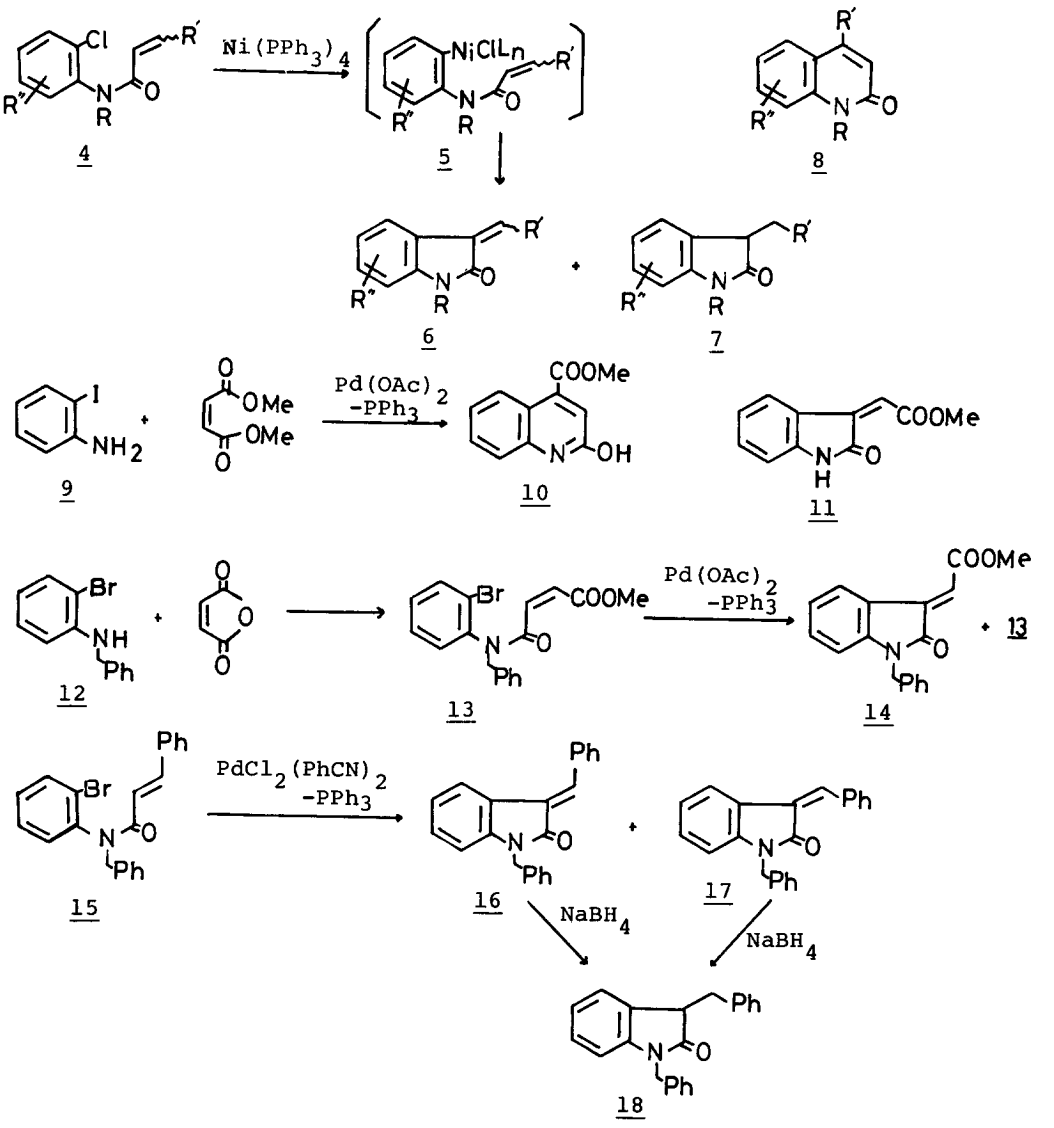


Chart 2

These compounds were easily reduced with sodium borohydride in ethanol to give 1,3-dibenzyl oxindole(18). In this case, the six membered benzolactam[8(R= CH_2Ph, R'=Ph, R"=H)] was also not detected.

Furthermore, the reaction of the compound(20) was investigated to locate which cyclization of 6-*Exo-Trig* or 7-*Endo-Trig* type should be predominant. The compound(20) which was prepared from N-(o-bromobenzyl)-benzylamine(19) by the same treatment as the synthesis of 13, was heated with $Pd(OAc)_2$ and PPh_3 in benzonitrile at 125° for 3 hr to give two compounds[21a, oil, m/e 307(M^+) and

21b, prisms, mp 137-139°, m/e 307(M^+)] in the yields of 18.6% and 28.7%, respectively. These compounds were verified to be the geometric isomers regarding the olefinic bond since either 21a or 21b was easily reduced with sodium borohydride in ethanol to give the same compound(22).

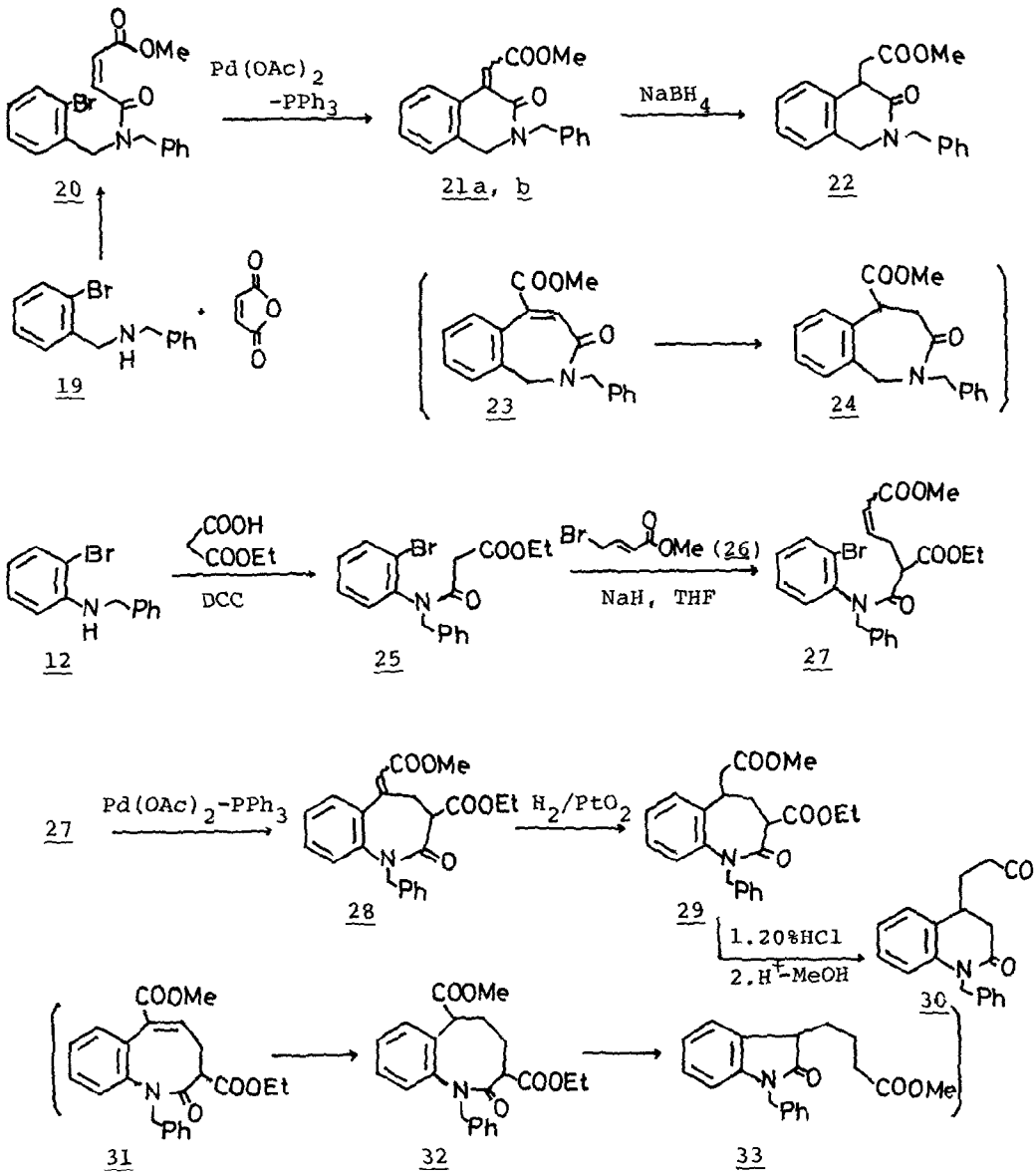


Chart 3

On the basis of the mass spectrum of 22[m/e 309(M^+), 278(M^+-OMe), 236(M^+-CH_2COOMe) and 91], it was presumed that this compound(22) contains a newly formed six-membered ring, since the mass spectrum of the assumed compound(24) which should have been obtained from 23, if it were produced, by the above reduction, could not indicate the peak of 236(M^+-CH_2COOMe). Therefore, 6-*Exo-Trig* cyclization can be assumed to have proceeded in the present case.

Attention was now turned to the cyclization of 27 which has two possibilities of yielding either seven or eight membered ring system. Thus, condensation of N-benzyl-o-bromoaniline(12) with ethoxycarbonyl acetic acid by use of dicyclohexylcarbodiimide(DCC) afforded the compound(25), which was reacted with methyl·γ-bromocrotonate(26) in the presence of sodium hydride in THF to give the objective substrate(27). The treatment of 27 with $Pd(OAc)_2$ and PPh_3 in benzonitrile at 120° for 6 hr gave the isomeric mixture of the cyclization product [28, m/e 393(M^+) and 321(M^+-COOEt), δ($CDCl_3$) 1.32(3H, t, J=7Hz, $-CH_2\underline{CH_3}$), 3.61 (3H, s, $OC\underline{H_3}$), 4.88 and 5.30(2H, d and d, J=16Hz, $NC\underline{H_2}Ph$), 6.40 and 6.50(1H, s and s, vinylic protons), 38.2% yield] along with the starting material(27, 25.7%). The product(28) was hydrogenated with PtO_2 in ethanol to give 29[oil, m/e 395(M^+), δ($CDCl_3$) 1.08(3H, t, J=7Hz, $-CH_2\underline{CH_3}$), 3.63(3H, s, $OC\underline{H_3}$), 4.87 and 5.18(2H, d and d, J=15Hz, $NC\underline{H_2}Ph$)], which was refluxed in 20% hydrochloric acid overnight and then followed by esterification with methanol to give the trans-cyclized product[30, mp 117.5-118°(from ether), ν($CHCl_3$) 1660 and 1730 cm^{-1}, m/e 323(M^+), 250(M^+-CH_2COOMe) and 91] in the yield of 70% from 30. These data clearly indicate that this compound(30) was the quinoline derivative, but not the oxindole(33), suggesting that the *Exo*-cyclization had occurred with 27, because if the cyclization had proceeded in an *Endo*-type, an eight-membered compound(31) would have been obtained, in which the transcyclization with 20% hydrochloric acid could be assumed to give the oxindole derivative(33).

These results demonstrate that the intra-molecular cyclization with aryl-palladium complexes proceeded in an *Exo*-type with 13, 15, 20 and 27. Further studies are in progress.

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References:

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