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THE NOVEL SYNTHETIC METHODS OF HETEROCYCLES—— INDOLES, QUINOLINES, ISOQUINOLINES, AND THE RELATED COMPOUNDS

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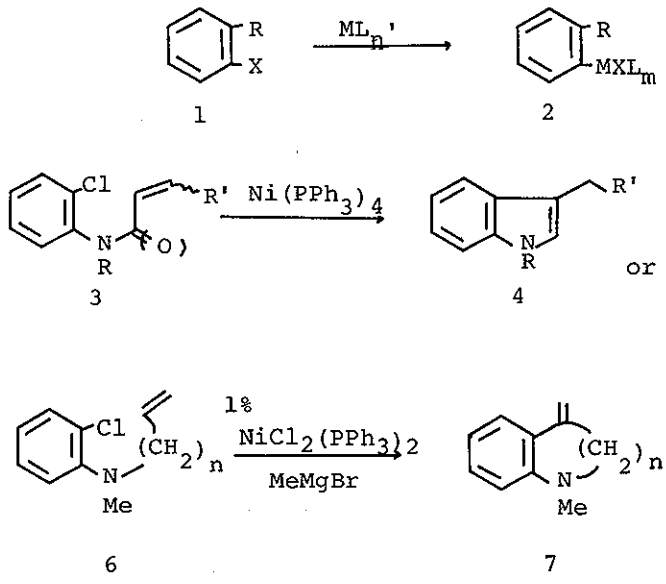
In order to create the novel synthetic methods of heterocycles such as indoles, quinolines and isoquinolines, (1) utilization of organometallic compounds, (2) the anodic oxidation of some lactams, (3) the Bischler-Napieralski reaction with the isonitriles and so on, have been investigated.

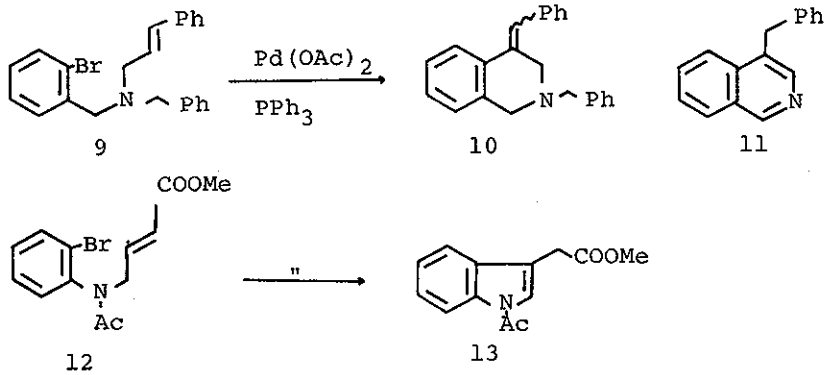
1. The utilization of organometallic compounds.

The arylmetal complex(2) which was prepared from aryl halide(1) and low valent metal(ML_n,) was proved to be an intermediate for the synthesis of heterocyclic compounds. Recently, we have reported the new synthetic method of indole(4) and oxindole derivative(5) by utilization of o-chloroaniline derivatives(3) and an equimolar amount of $Ni(PPh)_4$.[1] In this reaction, it was considered that a catalytic amount of $NiCl_2(PPh_3)_2$ should be required with the excess of Grignard reagent. Thus, when o-chloro-N-allyl-N-methylaniline(6, n=1) was reacted with MeMgBr(200 mol%) in the presence of a catalytic amount $NiCl_2(PPh_3)_2$(1 mol%) in tetrahydrofuran, 1,3-dimethyl indole(8) was obtained in a fairly

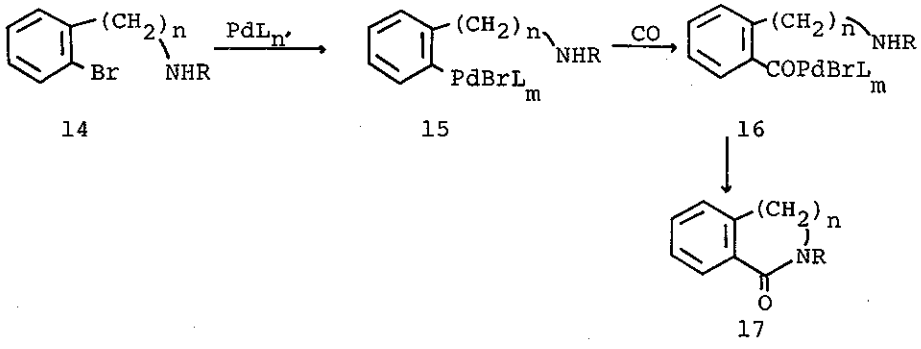
good yield(53.4%). Moreover, quinoline(7, n=2, 90.4%) and benzazepine derivatives(7, n=3, 62.0%) were obtained in good yields.



On the other hand, the palladium-catalyzed reaction seems to be the particularly fascinating field, and the palladium complexes have been utilized for this intramolecular cyclization.[2] The compound(9) was heated with a catalytic amount of $Pd(OAc)_2$ (2 mol%) and PPh_3(4 mol%) in the presence of tetrametylethylenediamine(TMED, 200 mol%) under nitrogen atmosphere at 125° for 69 h to furnish the hydroisoquinoline(10, 7.6%) and the isoquinoline(11, 27.3%). Similarly, 12 gave 13 in 43% yield.

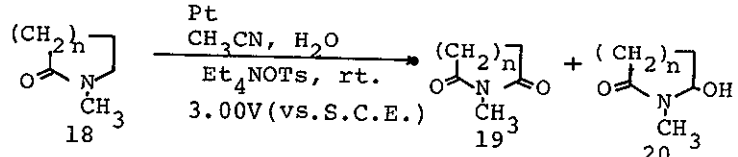


Subsequently, the carbonylation of the arylmetal complex(15) was tried with success to give the acylmetal complex(16), which reacted with the internal amino group to furnish the benzolactam (17). The compound(14, n=1, R=CH_2Ph) was heated with a catalytic amount of $Pd(OAc)_2$(2 mol%) and PPh_3(4 mol%) in the presence of n-Bu_3N(1.1mol) under the atmosphere of carbon monoxide at 100° for 26 h, to give an expected benzolactam(17, n=1, R=CH_2Ph) in 63% yield. Similarly, the six(17, n=2, R=CH_2Ph) and seven(17, n=3, R=CH_2Ph) membered benzolactams were obtained in 65 and 63% yields, respectively.



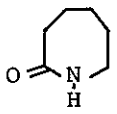
2. The anodic oxidation of some lactams

The anodic oxidation of N-methylcyclic lactams(18) in CH_3CN with Et_4NOTs as an electrolyte gave N-methylimides(19) and N-methylhydroxylactams(20) in moderate yields particularly in the case of (18, n=1,2). In a similar manner, oxidation of N-methylcaprolactam (18, n=3) afforded caprolactam (21) and N-hydroxymethyl caprolactam (22) in 22 and 19% yields, respectively. This type of reaction might be extended to the effective synthesis of some heterocycles.

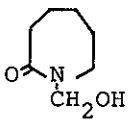


18 → 19 + 20

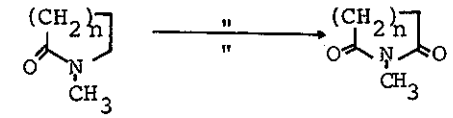
n	reaction time (h)	yield of 19 (%)	yield of 20 (%)
1	19.5	22.2	41.0
2	10.0	20.5	41.0
3	20.0	–	–



21 (22%)

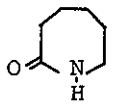


22 (19%)



23 → 24

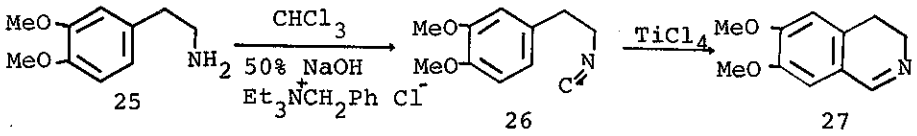
n	reaction time (h)	yield of 24 (%)
1	49	44.0
2	53	45.0
3	50	–



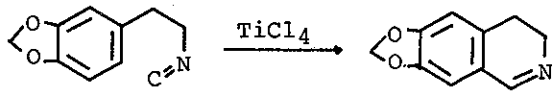
21 (35%)

3. The Bischler-Napieralski reaction with the isonitriles.

The isonitrile(26) which was prepared from 25 and dichlorocarbene was refluxed with Lewis acids such as BF_3Et_2O or $TiCl_4$ in methylene chloride to produce dihydroisoquinoline(27) in good yield($TiCl_4$,70%). Similarly, the compound(28) gave 29 in 30.6% yield.



25 26 27



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2. M.Mori, K.Chiba and Y.Ban, Tetrahedron Letters, 1037 (1977).