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COPPER(I) IODIDE-PROMOTED CYCLIZATION OF N-2-HALOARYL- AND N-(2-HALOARYL)METHYL-SUBSTITUTED ENAMINONES

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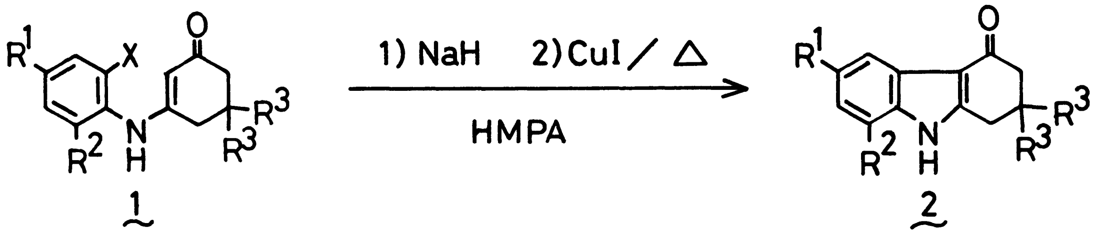
Anions derived from the title compounds are found to undergo smooth cyclization to give indoles and dihydroisoquinolines, respectively, on being heated in the presence of copper(I) iodide in hexamethylphosphoric triamide.

Recently, considerable attention has been focused on the development of new synthetic methods for the construction of nitrogen-containning heterocyclic systems such as indoles, quinolines, and isoquinolines, particularly under non-acidic conditions.[1] Among these, Kibayashi and his co-workers have reported that N-2-haloaryl-substituted enaminones are cyclized either via aryne intermediate,[2a] by photochemical activation,[2b] or by palladiumn catalyst.[2c] The cyclization reaction of enaminones is of interest in view of the readily available starting materials and versatile applicability to the synthesis of indoles, isoquinolines, and benzazepines.[3] In the course of our studies on copper(I) iodide-promoted arylation of anionic species,[4] we have found that N-2-haloaryl- and N-(2-haloaryl)methyl-substituted enaminones (1 and 6) undergo efficient cyclization to give indoles and dihydroisoquinolines, respectively, by the aid of copper(I) iodide in hexamethylphosphoric triamide (HMPA).



(1)

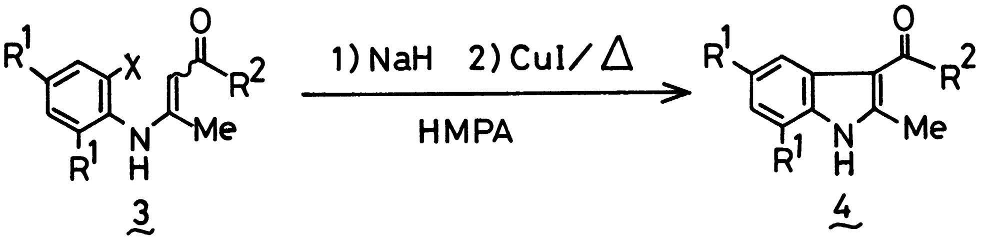
The procedure involves treatment of enaminones with sodium hydride in HMPA, followed by heating in the presence of 1.5-2.0 equiv of copper(I) iodide at 100-170°C for suitable time. After usual work-up, separation of the products over silica gel column gave cyclized products in moderate to good yields. Intramolecular cyclization of N-2-bromoaryl- and N-2-iodoaryl-substituted enaminones (1a-f) proceeded very efficiently to give carbazole derivatives in high yields (Table 1). N-2-bromoaryl-substituted enaminones required

Table 1. Copper(I) Iodide-promoted Cyclization of Enaminones 1 in HMPA

Enaminones	R^1	R^2	R^3	X	Temp. (°C)	Time (h)	Yields[a] (%)	Products; mp(°C)(lit. mp)
1a	H	H	Me	I	105-120	1	97	2a; 210-211(209-211)[b]
1b	H	H	Me	Br	160-170	3	92	2a
1c	H	H	H	I	105-120	1	82	2b; 223-227(227-228)[b]
1d	H	H	H	Br	160-170	3	80	2b
1e	Me	H	Me	I	125-130	2	98	2c; 255-257
1f	Me	Me	Me	I	110	7	92	2d; 275-278
1g	H	H	Me	Cl	160-180	6	4	2a
1h	H	H	H	Cl	160-180	6	6	2b

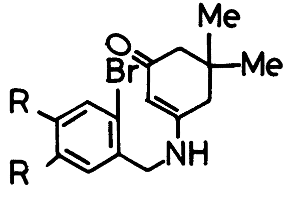
a, Isolated yields. b, Reference 2b.

slightly higher temperature than the corresponding iodo-compounds. N-2-Chlorophenyl-substituted enaminones 1g and 1h gave poor results. Similarly, enaminones 3a (R^1=H, R^2=Ph, X=Br) and 3b (R^1=R^2=Me, X=I) derived from acyclic β-diketones gave indoles 4a[5] and 4b in 63 and 34% yields, respectively. The order of reactivity of Ar-I > Ar-Br >> Ar-Cl is in good agreement with that observed in intermolecular copper(I) iodide-promoted arylation of anionic species.[4]



(2)

We next examined the reaction of a series of N-(2-bromoaryl)methyl-substituted enaminones 5 and 6. Although 5a (R=OMe) and 5b (R-R=OCH_2O) were almost consumed after 3 h at 100°, we were unable to obtain significant amounts of cyclized products. However, enaminones 6a (R^1=OMe, R^2=Me), 6b (R^1-R^1=OCH_2O R^2=Ph), and 6c (R^1-R^2=OCH_2O, R^2=Me) derived from acyclic β-diketone gave dihydroisoquinolines 7a, 7b, and 7c in 42, 43, and 67% yields, respectively. It is interesting to note that neither further oxidation to isocarbostyrils or dehydrogenation to isoquinolines, which was reported to be accompanied by the cyclization by the aryne reaction or photochemical methods,[2] were not observed under our conditions. Reluctance of 5a and 5b to cyclization might be ascribed to the enolates' conformation, which would be unfavorable for the cyclization process.



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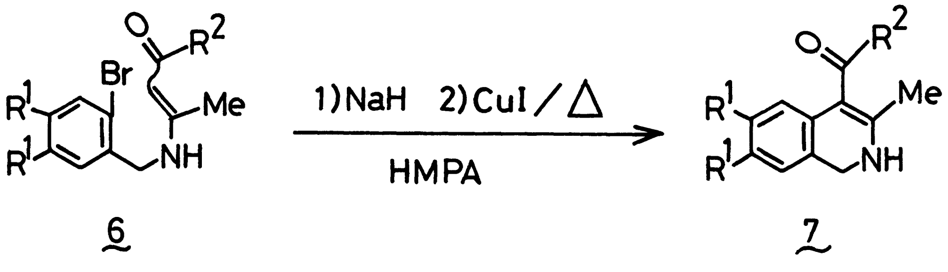

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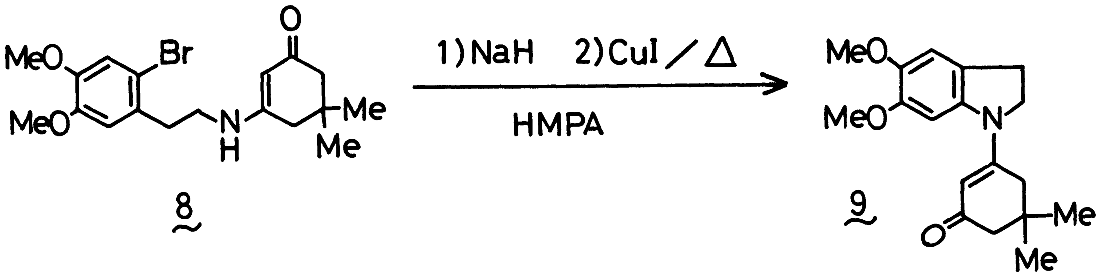
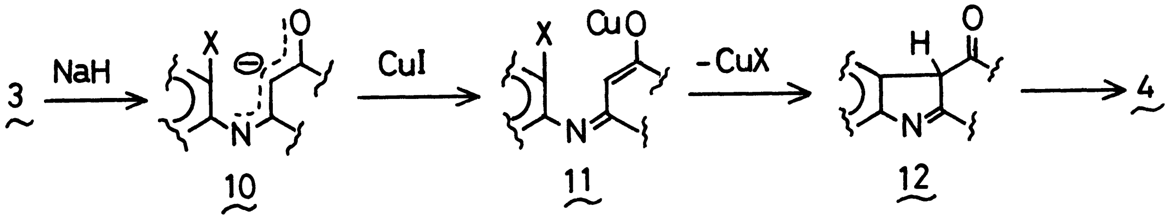


(4)

Further, we attempted the cyclization reaction of N-(2-bromoaryl)ethyl-substituted enaminone 8 to benzazepine. Unfortunately, it turned out that treatment of 8 with sodium hydride, followed by heating with copper(I) iodide produced indoline 9 exclusively in 88% yield via the nucleophilic attack of nitrogen.[2b] It might be said that this type of cyclization would provide a simple synthetic route to indoline derivatives.[6]

The mechanism of the copper(I) iodide-promoted cyclization of enaminones has not been studied yet. However, one may envision a possible role of copper-enolate such as 11. The stereochemistry of enaminones 3 and 6 derived from acyclic β-diketones has not been determined. E-configuration does not seem necessarily required for the cyclization, because free rotation may be expected in the deprotonated species such as 10 or 11. An indolenine 12 is probably an initial cyclization product, and then it undergoes aromatization as expected.



(5)

Consequently this procedure presents a convenient and high yield synthesis of indoles, carbazoles, dihydroisoquinolines, and indolines starting with the readily available materials. In comparison with the methods of the previous enaminones-cyclization, the copper(I) iodide-promoted cyclization has some advantages: good yields of products and simple manipulation as well as mild condition which suppresses further oxidation of 7.

A typical procedure is illustrated below for the preparation of 2,3-dihydro-2,2,6-trimethylcarbazol-4(1H)-one (2c); To a stirred suspension of sodiumn hydride (80 mg of a 60% suspension in mineral oil, 2 mmol; trituated with dry hexane) under a nitrogen atmosphere in 5 ml of HMPA at 25°C was added 3-(2-iodo-4-methylanilino)-5,5-dimethylcyclohex-2-en-1-one (1e) (355mg, 1 mmol). When hydrogen evolution has ceased, copper(I) iodide (380 mg, 2 mmol) is added. The mixture is heated at 125-130°C with stirring for 2 hours. After colling, the mixture is diluted with water and the product is extracted with ether. The extract is dried over anhydrous Na_2SO_4 and evaporated to give 2c as semi-solid materials. Chromatography on a silica gel column and recrystallization from chloroform-hexane gave 223 mg of 2c as white prisms. (98%).

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5) All new compounds gave satisfactory elemental analyses and spectral data. Selected data follow. 4a; ^{1}H-NMR($CDCl_3$) 2.47(s, 3H), 6.9-7.8(m, 9H), and 9.0(mobile, 1H). IR(KBr) 3200, 1600, 1565, 1450, 1420, 1220, and 750 cm^{-1}. 6a; mp 137-138°C; ^{1}H-NMR($CDCl_3$) 1.57(s, 3H), 1.90(s, 3H), 3.76(s, 3H), 3.86 (s, 3H), 4.00(d, J=5Hz, 2H), 4.8(mobile,1H), 6.60(s, iH), and 6.80(s, 1H); IR(KBr) 3400, 1605, 1560, 1410, 1300, 1260, and 750 cm^{-1}.

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