CHEMISTRY LETTERS, pp. 913-916, 1988.

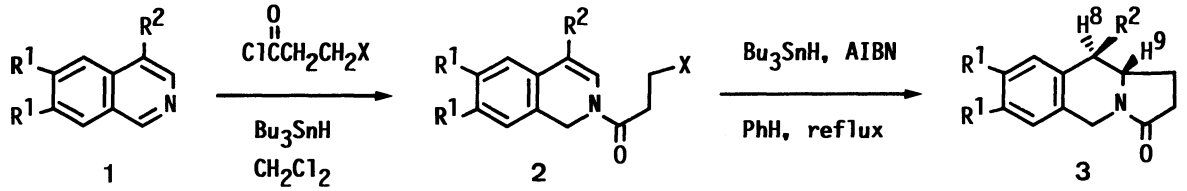
Synthesis and Radical Cyclization of 2-(β-Haloacyl)-1,2-dihydroisoquinolines by Means of Tin Hydride. One-Pot Synthesis of Benzo[f]indolizidine Systems from Isoquinolines

Ryohei YAMAGUCHI,* Takashi HAMASAKI, and Kiitiro UTIMOTO
Department of Industrial Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Kyoto 606

Reactions of isoquinolines activated by 2-halopropionyl chlorides with tributyltin hydride afford selectively 2-(2-halopropionyl)-1,2-dihydroisoquinolines in good yields, the radical cyclizations of which furnish benzo[f]indolizidine systems. The above two reactions can be consecutively achieved in one-pot. Furthermore, the present procedures are extended to synthesis of 12,12a-dihydroisoindolo[2,3-b]isoquinolin-5(7H)-one.

Radical cyclization has now been of growing interest for constructing hetero- and carbocyclic systems.[1] Intramolecular additions of α-amino radical to γ-unsaturated bond[2] and β-amino radical to β-unsaturated bond[3] have been widely used to form five-membered nitrogen rings. In contrast, addition reactions of γ-amino radical to α-double bond, i.e. enamine or enamide,[4] have received a little attention.[5] We have recently reported a simple access to a variety of N-acylenamine derivatives by a series of the highly chemo- and regio-selective reactions of organotin reagents with N-acylated nitrogen heteroaromatics.[6] Thus, it has been anticipated that the use of β-haloacyl chloride as an acylating agent would result in the formation of N-(β-haloacyl)enamine, which might cyclize to produce nitrogen five-membered ring under radical conditions. We wish to report here that the idea has been realized in the reactions with isoquinoline and that these two step sequences provide a new and facile route to benzo[f]indolizidine system, which consists of a partial structure of some alkaloids.[7]

We have already observed that since organotin reagents react with N-acylated nitrogen heteroaromatics very chemoselectively, the quarternary salts are not necessarily prepared in advance.[6] When 2-iodopropionyl chloride was added to a mixture of isoquinoline (**1a**) and tributyltin hydride in dichloromethane at -78 °C, the reaction proceeded very smoothly to give 2-(2-iodopropionyl)-1,2-dihydroisoquinoline (**2a**)[8,9] in 94% yield (Scheme 1). This result shows that tin hydride very selectively reduces the N-acylisoquinolinium salt produced in situ and does only trace, if any, of the acid chloride itself[10] or iodo group. The reactions of substituted isoquinolines (**1**) also proceeded very well, as shown in Table 1. Tolerance of cyano and methoxycarbonyl groups demonstrates the versatility of the present reaction.



Scheme 1.

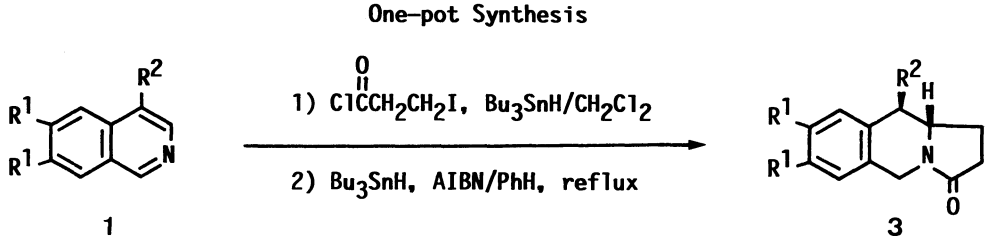
2-(2-Iodopropionyl)-1,2-dihydroisoquinoline (**2a**) thus obtained was subsequently subjected to radical cyclization reaction. When a dilute solution of **2a** and tributyltin hydride in the presence of catalytic amount of azobis-iso-butyronitrile (AIBN) was heated under reflux, the cyclization took place at the α-position of enamine moiety to furnish benzo[f]indolizidin-3-one (**3a**)[11] in 62% yield. The results of other examples are added in Table 1.[12] Thus, the above two step sequences provide an easy access to benzo[f]indolizidine system.

Table 1. Reactions of Isoquinolines with Tributyltin Hydride in the presence of 2-Halopropionyl Chlorides and Subsequent Radical Cyclizations

Entry	R^1	R^2	X	Temp/°C	Product	Yield/%[a]	Product	Yield/%[a]
1	H	H	I	-78	**2a**	94	**3a**	62
2	H	H	Br	-78	**2a**	92	**3a**	45
3	H	CN	I	0	**2b**	83	**3b**	81
4	H	CO_2Me	I	0	**2c**	84	**3c**	73
5	OMe	H	I	-78	**2d**	60[b]	**3d**	62

a) Isolated yield. b) Three equiv. of Bu_3SnH was used.

The successful cyclization has prompted us to examine an one-pot synthesis of benzo[f]indolizidine system, because the both sequences use tin hydride. Thus, after the first step, i.e. reductive acylation, finished, the second step, i.e. radical cyclization was conducted by adding tributyltin hydride, AIBN, and benzene to the reaction mixture (Scheme 2). The results are summarized in Table 2.



Scheme 2.

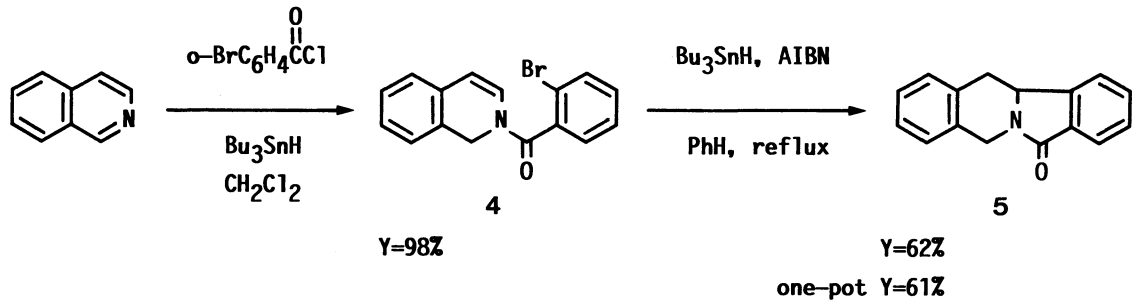
Table 2. One-Pot synthesis of Benzo[f]indolizidin-3-ones

Entry	R^1	R^2	Product	Yield/%[a)]
1	H	H	**3a**	56
2	H	CN	**3b**	60
3	H	CO_2Me	**3c**	40
4	OMe	H	**3d**	32

a) Isolated yield.

Typical experimental procedures are as follows (one-pot synthesis): To a solution of isoquinoline (1 mmol) and Bu_3SnH (1 mmol) in CH_2Cl_2 (6 mL) was added 2-iodopropionyl chloride (1.1 mmol) at -78 °C and the mixture was stirred at that temp for 2 h and then warmed to room temp. To the reaction mixture was added Bu_3SnH (1.2 mmol), PhH (50 mL), and AIBN (20 mg) and the mixture was heated at reflux for 48 h. The solvent was evaporated and the residue was chromatographed on silica gel to give **3a**[11] (105 mg, 56%): IR (neat) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00-7.43 (m, 4H), 4.91 (d, 1H, J=18 Hz), 4.20 (d, 1H, J=18 Hz), 3.56-3.93 (m, 1H), 1.50-3.26 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.0 (s), 131.7 (s), 131.1 (s), 129.0 (d), 126.6 (d), 126.5 (2d), 53.8 (d), 42.4 (t), 36.7 (t), 30.0 (t), 25.2 (t).

Furthermore, the present procedures can be extended to synthesis of 12,12a-dihydroisoindolo[2,3-b]isoquinolin-5(7H)-one (**5**)[13] through the isolation of 2-(o-bromobenzoyl)-1,2-dihydroisoquinoline (**4**) or in one-pot, when o-bromobenzoyl chloride is used as the acylating agent, as shown in Scheme 3.



Scheme 3.

In summary, we have demonstrated the short and simple route to benzo[f]-indolizidine systems from isoquinolines by means of organotin reagent. Further studies on organotin methodology for constructing nitrogen heterocycles are under ways.

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8) Mp 79-80 °C; IR (nujol) 1665, 1635, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87-7.37 (m, 4H), 6.60 (d, 1H, J=8 Hz), 5.82 (d, 1H, J=8 Hz), 4.84 (d, 2H, J=13.5 Hz), 3.37 (t, 2H, J=7 Hz), 2.99 (t, 2H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ 168.3 (s), 130.2 (s), 129.4 (s), 127.6 (d), 127.4 (d), 125.8 (d), 124.7 (d), 110.4 (d), 44.4 (t), 37.4 (t), -3.2 (t).

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(Received February 19, 1988)