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Allylboration of functionalized isoquinolines

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Abstract

Functionalized isoquinolines react with triallylborane to produce 1,3-diallylated 1,2,3,4-tetrahydroisoquinolines **1**–**8** with excellent chemo- and stereoselectivity. In these conditions 4-bromoisoquinoline was converted into tricyclic aziridine **10**. Synthesis of monoallylated tetrahydroisoquinolines using allyldipropylborane and reduction with $NaBH_4$ was also developed. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Isoquinolines; Boranes; Allylation; Allylboration; Stereoselectivity; Aziridines

1. Introduction

1,2-Addition of organometallic reagents to the C=N double bond is a classical reaction widely used in organic synthesis [1,2]. Thus, allylboration [2–7] of imines is an accustomed method for synthesis of butenylamines of diverse constitution.

Several aromatic nitrogen heterocycles e. g. quinolines and phenanthridine react with allylboranes in a way analogous to imines to give the products of addition to the C=N bond. Deboronation of aminoboranes formed leads to 2-allyl-1,2-dihydroquinolines (85–95%) and 5-allyl-5,6-dihydrophenanthridine [8], respectively. Isoquinoline is also easily allylborated with triallylborane (All_3B) [9]. Subsequent action of alcohol (1 h, 20 °C) and alkali solution afford *trans*-1,3-diallyl-1,2,3,4-tetrahydroisoquinoline **A**. It should be noted, that in this unusual transformation the alcohol is an essential reagent, but not just a solvent.

Allylboration is also a key step in synthesis of unsymmetrically substituted *trans*-1-R-3-allyl-1,2,3,4-tetrahydroisoquinolines (R = Alk, Ar) from isoquinoline, RLi and All_3B [10].

All the above mentioned reactions proceed with allylic rearrangement seemingly via six-membered chair-like transition state [7].

Recently, we have found that isoquinolines react easily with allylzinc bromide giving either **A** or benzoisoquinuclidine derivative depending on the reaction conditions [11].

In order to expand the scope of application for the reaction of isoquinoline with triallylborane, we decided to introduce a range of functionalized isoquinolines into it.

2. Results and discussion

Isoquinolines bearing large variety of substituents are transformed into *trans*-1,2-diallyl-1,2,3,4-tetrahydroisoquinolines under the action of allylic boranes. These reactions proceed in mild conditions, with high chemoselectivity.

Such substituents as halogen, amino-group, and even easily reduced by allylboranes cyano- and nitro-groups are left unchanged under the experimental conditions.

It is known that aliphatic and aromatic nitriles readily react with triallylborane giving (after work-up) α,α-diallylamines [4]. We carried out the reaction of 5-cyanoisoquinoline with All_3B at −35 °C and isolated only the product of isoquinoline ring allylboration **2**.

Aromatic nitro-compounds react with All_3B at 80 °C radically, giving the products of partial reduction of nitro-group [12]. At −35 °C the reaction of 5-nitroisoquinoline with 1 equivalent of All_3B does not involve

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nitro-group, and compound **3** was isolated after deboronation in 95% yield.

Tris(2-methyl-2-propenyl)borane (trimethallylborane) reacts with isoquinoline analogously to All_3B giving the corresponding *trans*-1,3-dimethallyl-1,2,3,4-tetrahydroisoquinolines (**7** and **8**) with high stereoselectivity (Scheme 1).

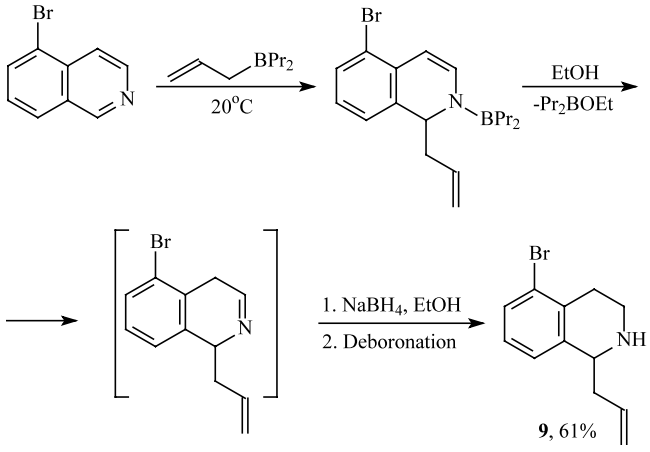
A possible mechanism of allylboration of isoquinolines is shown in Scheme 2.

In the first step, the allylborane addition to the 1,2 C=N bond of isoquinoline takes place. In the second, key step, the stable intermediate **C** undergoes rearrangement under the action of electrophile, such as isopropyl alcohol. In the course of this rearrangement enaminoborane **C** is transformed into iminoborane **D**, in which the imino-function is immediately allylborated [7] resulting in **E**. The deboronation method used in the last step of this one-pot procedure depends on the substituents in the isoquinoline ring. For example, the cyano-group is labile to the aqueous NaOH, so in case of 5-cyanoisoquinoline the mild deboronation procedure using diethanolamine was used.

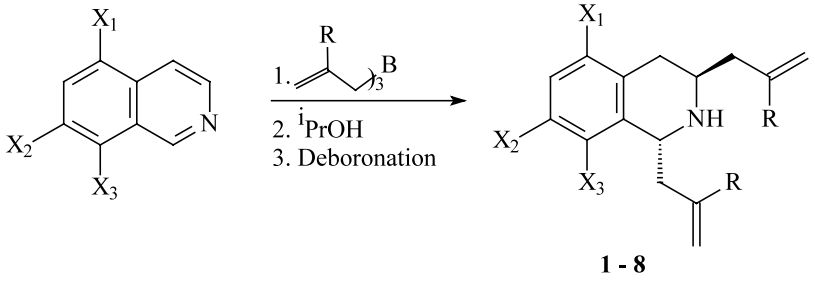
Basing on the above mechanism, we decided to carry out monoallylation of 5-bromoisoquinoline with allyldipropylborane (Scheme 3).

On the first stage of this reaction allyldipropylborane adds to 5-bromoisoquinoline forming an enamine analogous to **C**, which undergoes rearrangement into imine under the action of alcohol. Dipropyl(ethoxy)borane formed is unreactive to imines (unlike diallyl(alkoxy)borane), so the intermediate imine can be introduced into the reaction with $NaBH_4$ to produce (after deboronation) the corresponding amine **9**.

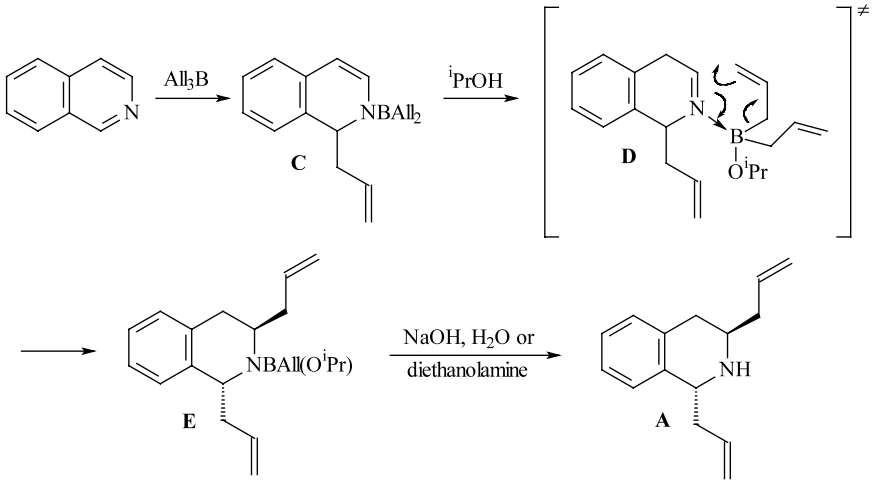
The most interesting result was obtained when 4-bromoisoquinoline was consequently treated with All_3B, and the mixture $^{i}PrOH–Et_3N$ (Scheme 4).



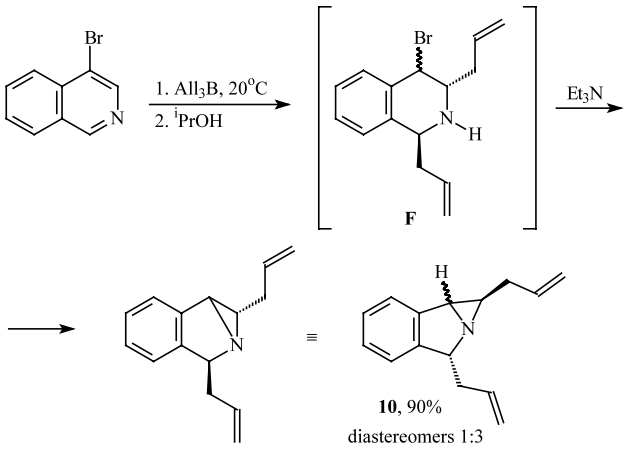
Scheme 3. Synthesis of monoallylated 1,2,3,4-tetrahydroisoqionoline.



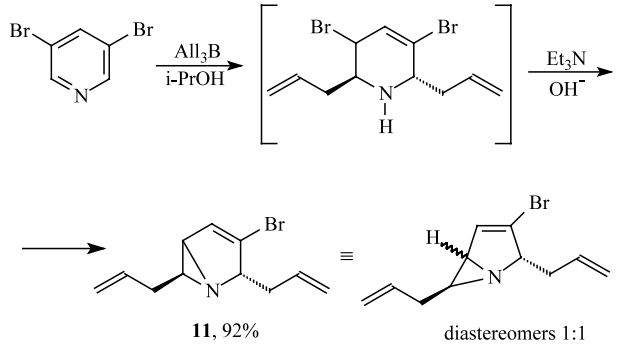
Scheme 1. Chemoselective allylboration of functionalized isoquinolines.



Scheme 2. Possible mechanism of allylboration of isoquinolines.



Scheme 4. Aziridine formation from 4-bromoisoquinoline.



Scheme 5. Aziridine formation from 2,5-dibromopyridine.

The intermediate β-bromoamine **F** formed after diallylboration undergoes cyclization into aziridine **10** under the action of base. As 1- and 3-allylic groups are always in *trans*-position to each other, **10** is a mixture of only two diastereomers in a 1:3 ratio (NMR), differing in orientation of the aziridine ring relative to 1-allylic group.

3-Bromopyridine presents a system, analogous to 4-bromoisoquinoline. However, 3-bromopyridine reacts with All_3B giving *trans*-2,5-diallyl-3-bromo-1,2,5,6-tetrahydropyridine [13]. At the same time, consequent treatment of 3,5-dibromopyridine with triallylborane and Et_3N–^{i}PrOH afforded bicyclic aziridine **11** as a mixture of diastereomers 1:1 in 92% yield (Scheme 5).

3. Experimental

3.1. General remarks

All operations with organoboron compounds were carried out in a dry argon atmosphere. Absolute THF, benzene and ^{i}PrOH were used. NMR ^{1}H and ^{13}C spectra were recorded on Bruker AC-200P and AM-300 instruments. Mass-spectra were obtained on a VARIAN-MAT instrument.

3.2. *trans*-1,3-Diallyl-5-bromo-1,2,3,4-tetrahydroisoquinoline (**4**) (general procedure)

Triallylborane (4.6 ml, 26 mmol) was added to the solution of 5-bromoisoquinoline (5.0 g, 24 mmol) in 25 ml benzene with stirring. The dark-red coloration of the reaction mixture appeared for several seconds, and then disappeared. The solution was refluxed for 30 min, cooled to 0 °C, worked up with isopropanol (6.2 ml, 72 mmol) and refluxed for 2 h. Then 5 M NaOH was added and the mixture was vigorously stirred until complete deboronation (no green coloration of flame) of the organic layer ($\approx$30 min). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 10 ml). Combined organic extracts were dried with K_2CO_3 and concentrated. Distillation (136–137 °C/0.5 Torr) gave **4** (6.51 g, 92%).

3.3. *trans*-1,3-Diallyl-5-amino-1,2,3,4-tetrahydroisoquinoline (**1**)

Two equivalents of triallylborane were used. Yield: 95%, melting point (m.p.) 89–90 °C.

Table 1
Experimental data

Compound	X_1	X_2	X_3	R	Yield (%)	B.p. (°C Torr^{-1})	M.p. (°C)	n_D^{20}
1	NH_2	H	H	H	95	–	89.5–90	–
2	CN	H	H	H	86	–	62–63	–
3	NO_2	H	H	H	95	–	68–69	–
4	Br	H	H	H	92	136–137/0.5	169–170[a]	1.5714
5	Br	Br	Br	H	82	–	62–63	–
6	Br	H	Br	H	75	168–170/0.5	215–216[a]	1.6134
7	H	H	H	Me	95	142–143/0.5	177–179[a]	1.5382
8	Br	H	H	Me	90	153–154/0.5	206–207[a]	1.5590
9					61	123–125/0.5	214–215[a]	–
10					90	95–96/0.5	–	1.5429

[a] Melting point given for hydrochloride.

Table 2
Elemental analysis data

Compound	%C Calc./Found	%H Calc./Found	%N Calc./Found
1	78.90/78.95	8.83/8.92	12.27/12.23
2	80.63/80.69	7.61/7.69	11.75/11.69
3	69.74/69.71	7.02/7.09	10.84/10.74
4	61.65/61.62	6.21/6.30	4.79/4.68
5	40.04/39.94	3.58/3.64	3.11/3.07
6*HCl	44.20/44.30	4.45/4.50	3.44/3.49
7	84.59/84.45	9.60/9.65	5.80/5.63
8	63.75/63.79	6.92/6.97	4.37/4.20
9*HCl	49.94/49.93	5.24/5.30	4.85/4.78
10	85.26/85.40	8.11/8.08	6.63/6.07

Table 3
Mass-spectroscopic data

Compound (M_r)	Mass spectrum m/z (I_{rel}, %)
1 (228)	228(2); 187(100); 158(6); 145(86); 129(15); 117(11); 91(8); 72(14); 58(24); 43(34)
2 (238)	197(19); 187(16); 154(15); 144(26); 58(64); 43(100); 41(10)
3 (258)	217(100); 187(9); 176(18); 175(18); 170(21); 159(80); 143(27); 129(60); 58(18); 43(29)
4 (292)	252, 250(100); 210, 208(97); 211(30); 170(12); 153(13); 143(100; 130(72); 129(68); 58(59); 41(55)
5 (450)	409(100); 368(32); 287(7); 208(9); 130(7); 58(66); 43(100)
7 (241)	241(1); 186(63); 144(32); 130(63); 115(30); 103(45); 91(40); 76(37); 55(40); 41(45)
8 (320)	266, 294(96); 210, 208(100); 170(17); 168(14); 143(12); 129(60); 115(11); 55(14); 40(21)
10 (211)	211(42), 210(47), 184(13), 170(100), 167(83), 157(15), 155(37), 143(43), 130(54), 128(40), 117(39), 58(44), 43(55), 41(49)

3.4. trans-1,3-Diallyl-5-cyano-1,2,3,4-tetrahydroisoquinoline (**2**)

To the solution of 5-cyanoisoquinoline (1.0 g, 6.5 mmol) in 20 ml THF triallylborane (1.2 ml, 6.7 mmol, 1.03 equivalents) was added at −35 °C with stirring. The mixture was allowed to warm to room temperature (r.t.), after 30 min it was cooled to −10 °C and isopropanol (1.6 ml, 20 mmol) was added. The solution stayed for 12 h at r.t., then worked up with diethanolamine (7.8 mmol) and the mixture was left at r.t. for 10 h. The crystalline solid (borate complex with diethanolamine) was filtered off and washed with hot hexane. The combined filtrate was concentrated in vacuo, diluted with hexane and filtered from solid borate complex. Hexane was removed in vacuo and the solid obtained was recrystallized from hexane, giving **2** (1.3 g, 86%) as yellow needles (m.p. 62–63 °C).

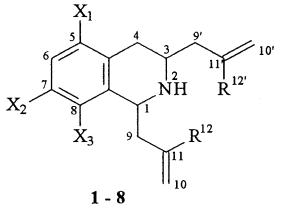
3.5. trans-1,3-Diallyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (**3**)

Compound **3** was obtained analogously to **2**, deboronation analogous to **4**. Yield: 95%, m.p. 68–69 °C.

3.6. 1-Allyl-5-bromo-1,2,3,4-tetrahydroisoquinoline (**9**)

To the solution of 5-bromoisoquinoline (6.0 g, 29 mmol) in 30 ml THF allyldipropylborane (5.2 ml, 29 mmol) was added dropwise with stirring. The mixture was stirred 1 h at r.t., then $NaBH_4$ (2.2 g, 58 mmol) and absolute ethanol (50 ml) were added. After stirring for 5 h, 10 ml H_2O was added and the mixture was refluxed

Table 4
^{13}C chemical shifts (ppm)



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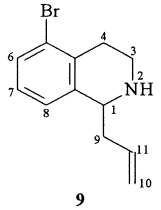

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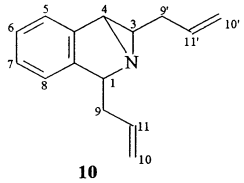

10

Compound	1	3	4	C_{Arom}–H	$C_{Arom.\ quaternary}$	9, 9′	10, 10′	11, 11′	12, 12′
1	54.9	45.2	30.5	112.3, 117.9, 125.8	119.2, 139.0, 143.9	40.6, 41.1	117.1, 117.6	134.9, 135.8	–
2	54.7	45.1	34.3	125.9, 130.8, 131.4	112.5, 138.3, 139.9	40.8, 40.6	118.3, 118.9	134.4, 134.9	–
3	55.1	44.9	32.8	122.5, 125.9, 131.7	129.9, 141.3, 149.2	40.7, 40.9	118.1, 118.8	134.4, 134.8	–
4	55.2	45.7	36.5	126.1, 126.8, 130.1	125.4, 134.1, 140.9	40.9	118.0, 118.5	134.8, 135.3	–
5	57.5	44.8	41.0	134.3 [a]	123.6, 124.9, 128.2, 135.2, 142.4	36.0, 36.4	118.4, 118.5	134.3*, 134.8	–
6	56.0	45.1	41.0	131.4 [a]	121.7, 124.7, 136.4, 140.1	36.2, 36.7	118.2, 118.3	134.4, 135.0	–
7	52.8	43.7	36.4	125.5, 125.9, 127.0, 128.8	134.6, 138.5	45.4*	113.4, 113.6	142.0, 142.7	22.0, 22.4
8	53.1	43.5	37.1	126.2, 126.7, 130.0	125.2, 134.4, 141.1	45.0, 45.3	113.6, 113.9	141.7, 142.2	21.9, 22.3
9	55.1	40.4	30.6	125.1, 126.8, 130.0	125.7, 135.0, 141.3	40.3	118.1	135.1	–
10 major isomer	64.0	47.7	26.0	122.1, 123.5, 127.0, 127.1	138.0, 146.2	42.2, 42.3	116.0, 117.0	135.1, 135.8	–

[a] Merged peaks.

Table 5
^{1}H Chemical shifts (ppm) and coupling constants (Hz)

Compound	1	2	3	4	4′	5	6	7	8	9, 9′	10, 10′	11, 11′	12, 12′
1	4.0dd $J = 4$; 10	2.05br. s	3.15m	1.9–2.6m	1.9–2.6m	3.55br. s (NH_2)	6.55m	7.0m	6.55m	1.9–2.6m	5.15m	5.85m	–
2	4.05dd $J = 4.2$; 9.8	2.05br. s	3.15m	3.05dd $J = 4.1$; 17.3	2.65dd $J = 17.3$; 10.3	–	7.5d $J = 7.7$	7.2–7.4m	7.2–7.4m	2.1–2.55m	5.15m	5.85m	–
3	4.15dd $J = 4.0$; 9.9	2.0br. s	3.05m	3.0dd $J = 3.7$; 17.3	2.8dd $J = 10.3$; 17.3	–	7.8d $J = 7.7$	7.3m	7.4d $J = 7$	2.1–2.6m	5.15m	5.9m	–
4	4.05dd $J = 4$; 9.9	2.05s	3.15m	2.85dd $J = 4.1$; 16.9	2.55dd $J = 9.6$; 16.9	–	7.4d $J = 7.3$	7.05m	7.05m	2.1–2.45m	5.15m	5.9m	–
5	4.25dd $J = 2$; 11	1.9–2.5m	3.4m	2.85dd $J = 4.4$; 17.6	2.65d $J = 14.3$	–	7.75s	–	–	1.9–2.5m	5.15m	5.8m	–
6*HCl	4.85m	9.45; 10.92s	3.65br. s	3.2dd $J = 5.5$; 18.0	2.6–3.1m	–	7.35AB $J = 8.5$	7.35AB $J = 8.5$	–	2.6–3.1m	5.25m	5.9m	–
7	4.20dd $J = 2.3$; 10.8	2.0–2.7m	3.2m	2.75dd $J = 3.3$; 16.2	2.0–2.7m	7.1m	7.1m	7.1m	7.1m	2.0–2.7m	4.85m	–	1.80s, 1.87s
8	4.15dd $J = 2.7$; 10.8	2.0–2.45m	3.2m	2.85dd $J = 3.6$; 17	2.55dd $J = 11.1$; 14.0	–	7.4dd $J = 1.7$; 7.2	7.0m	7.0m	2.0–2.45m	4.85m	–	1.78s, 1.85s
9*HCl	4.6s	9.7; 9.92s	3.4; 3.62s	3.2m	–	–	7.55dd $J = 1.5$; 7	7.1m	7.1m	2.9m	5.3m	5.85m	–
10 (2 diastereomers)	4.05m	–	3.57m	1.5–2.7m	–	7.0–7.4m	7.0–7.4m	7.0–7.4m	7.0–7.4m	1.5–2.7m	4.9–5.2m	5.6–6.0m	–

for 30 min. Then 6 M NaOH (50 ml) and H_2O_2 30% (15 ml) were consequently added with stirring. The reaction mixture was stirred until complete deboronation of the organic layer (flame probe). Standard extractive workup and distillation in vacuo gave 4.4 g (61%) of **9** as a viscous colorless oil (boiling point (b.p.) 123–125 °C/0.5 Torr). For further purification the product was transformed into hydrochloride, m.p. = 214–215 °C from EtOAc–MeOH.

3.7. Aziridine **10** (mixture of diastereomers)

To the solution of 4-bromoisoquinoline (2.0 g, 14 mmol) in 20 ml of hexane–THF mixture 1:1, triallylborane (2.6 ml, 15 mmol) was added dropwise with stirring. After 1 h stirring, the mixture of 1.6 ml NEt_3 and 2.5 ml ^{i}PrOH was added, and the resulting solution was heated at 45 °C for 5 h. Deboronation procedure analogous to **4**, extractive workup and distillation gave 2.7 g (90%) of **10** (b.p. 95–96 °C/0.5 Torr) (Tables 1–5).

Acknowledgements

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