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FACILE PREPARATION OF 1,2-DIHYDROISOQUINOLINES FROM *N*-BENZYLSULFONAMIDES AND BROMOACETYLENES

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This paper is dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday.

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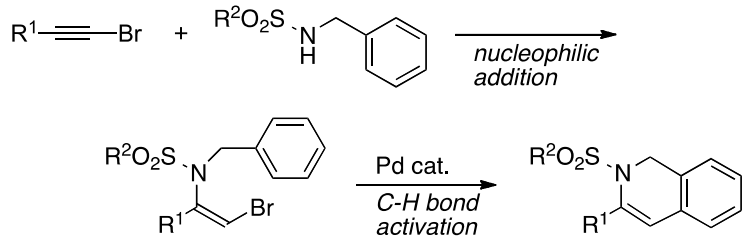
Abstract – Nucleophilic addition of *N*-benzylsulfonamides to 1-bromo-1-alkynes proceeded in a highly regio- and stereoselective manner to give (*Z*)-*N*-benzyl-*N*-(1-bromo-1-alken-2-yl)sulfonamides. These adducts cyclized via Pd-catalyzed aromatic C-H bond activation to afford 1,2-dihydroisoquinolines in good yields.

Nucleophilic addition to acetylenes having an electron-withdrawing group is a useful way to prepare functionalized olefins.[1] Nonetheless, haloacetylenes (halo = Cl, Br, or I) have not been amply investigated in these reactions, because halogens are generally considered as quite weak electron-withdrawing groups.[2-7] We have recently reported that 1-halo-1-alkynes underwent the nucleophilic addition with a few nitrogen nucleophiles such as imidazoles, imidazolines, or sulfonamides[8] to give stereo-defined haloolefines.[5f-h] We also demonstrated that these olefinic adducts are quite useful starting materials for the synthesis of nitrogen heterocycles.[5f,g] Considering the convenience in the preparation of these heterocyclic compounds, we report herein that an alternative nucleophile, *N*-benzylsulfonamide, is amenable to the nucleophilic addition to haloacetylenes and their adducts to a subsequent palladium-catalyzed cyclization,[9] as shown in Scheme 1. This overall reaction allows a novel

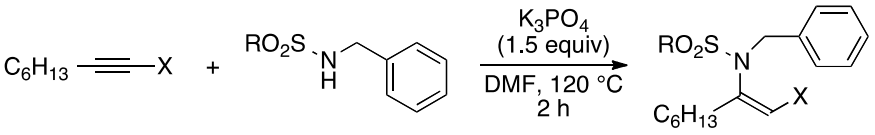


Scheme 1. Preparation of heterocyclic compounds via nucleophilic addition and cyclization

synthesis of 1,2-dihydroisoquinolines, which are frequently-found constituents in naturally occurring products and artificial pharmaceuticals.[10,11]

The first nucleophilic addition was examined with various 1-halo-1-alkynes **1**-**3** and representative *N*-benzylsulfonamides **4**-**7** (Table 1). Among the three haloacetylenes **1**-**3**, bromoacetylene **2** showed the best result under the similar reaction conditions reported previously by us,[5f] giving **9** in good yield (Table 1, entry 2). Chloroacetylene **1** could be also used albeit giving a somewhat lower yield, but iodoacetylene **3** could not (entries 1 and 4). The addition products **8** and **9** were obtained virtually as a single olefinic isomer as depicted in Table 1, and other isomers were not detected in the crude reaction mixture. The amount of **4** may be reduced from 3 to 2 equiv, if the slight decrease in the product yield is acceptable (entries 2 and 3). Alternatively, an excess portion of **4** was recovered in good yield and could be recycled (entry 2). As far as sulfonamides **4**-**7** are concerned, these gave almost similar yields

Table 1. Fundamental data for the nucleophilic addition



(**1**)-(**3**) (1 equiv) (**4**)-(**7**) (**8**)-(**13**) single isomer

Entry	Haloacetylene		Sulfonamide			Product		Recovered
	X		R		equiv		Yield (%)[a]	**4** (%)[b]
1	Cl	**1**	Et	**4**	3	**8**	63	--
2	Br	**2**	Et	**4**	3	**9**	69, 76[c]	91
3[d]	Br	**2**	Et	**4**	2	**9**	63	--
4	I	**3**	Et	**4**	3	**10**	0	--
5	Br	**2**	Me	**5**	3	**11**	67	--
6	Br	**2**	*n*-Bu	**6**	3	**12**	67	--
7	Br	**2**	*i*-Pr	**7**	3	**13**	61	--

[a]Isolated yield based on haloacetylene. [b]Isolated yield based on unreacted **4**. [c]Yield based on consumed **4**. [d]The reaction period was extended to 3 h.

(entries 2 and 5-7), irrespective of the size of their alkyl groups (R). The final choice of the ethyl group as the standard substituent was made based on the efficiency of the next cyclization step, which is discussed below.

Having obtained the adducts from haloacetylenes and *N*-benzylsulfonamides as shown in Table 1, we then examined their intramolecular cyclization (the second transformation in Scheme 1). When mesyl derivative **11** was treated with $Pd(OAc)_2$ under the same reaction conditions as reported previously,[5g] the desired ring closure via aromatic C-H bond activation was sluggish to give dihydroisoquinoline **14** only

Table 2. Fundamental data for intramolecular cyclization of bromoolefins **9** and **11-13** to afford 1,2-dihydroisoquinolines

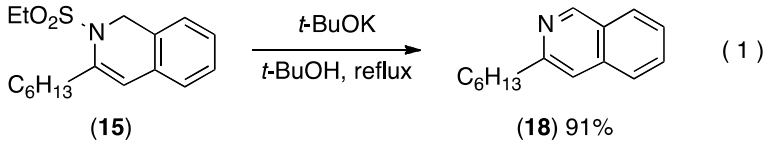
(**9**), (**11**)-(**13**) (**14**)-(**17**)

Entry	Bromoolefin R		$Pd(OAc)_2$ (mol%)	Ligand (mol%)	Base (equiv)	Period (min)	Product	Yield (%)[a]	Recovered **9**, **11-13** (%)[a]
1	Me	**11**	10	PCy_3 (30)	K_2CO_3 (2)	300	**14**	(8)	(63)
2	Me	**11**	10	P(2-Tol)$_3$ (30)	K_2CO_3 (2)	30	**14**	(12)	(88)
3	Me	**11**	10	P(2-furyl)$_3$ (30)	K_2CO_3 (2)	30	**14**	(16)	(84)
4	Me	**11**	10	P(*t*-Bu)$_3$•HBF_4 (30)	K_2CO_3 (2)	30	**14**	(5)	(95)
5	Me	**11**	10	dppe (15)	K_2CO_3 (2)	30	**14**	(40)	(17)
6	Me	**11**	10	PPh_3 (30)	K_2CO_3 (2)	30	**14**	(50)	(0)
7	Me	**11**	10	PPh_3 (30)	K_3PO_4 (2)	30	**14**	(39)	(29)
8	Me	**11**	10	PPh_3 (30)	Cs_2CO_3 (2)	30	**14**	(47)	(29)
9	Me	**11**	10	PPh_3 (30)	KOAc (2)	30	**14**	59 (60)	(0)
10	Me	**11**	10	PPh_3 (30)	KOAc (2)	45	**14**	60 (72)	(0)
11	Et	**9**	10	PPh_3 (30)	KOAc (2)	45	**15**	73 (77)	(0)
12	*n*-Bu	**12**	10	PPh_3 (30)	KOAc (2)	45	**16**	68 (68)	(0)
13	*i*-Pr	**13**	10	PPh_3 (30)	KOAc (2)	45	**17**	(59)	(17)
14	Et	**9**	10	PPh_3 (30)	KOAc (3)	45	**15**	80 (83)	(0)
15	Et	**9**	8	PPh_3 (24)	KOAc (3)	120	**15**	(75)	(4)
16	Et	**9**	5	PPh_3 (15)	KOAc (3)	480	**15**	(62)	(23)

[a]Isolated yield based on bromoolefin. The value in parentheses was determined by ^{1}H NMR spectroscopy using an internal standard.

in 8% yield (entry 1, Table 2). After searching for better combinations of phosphine ligand and base (entries 2-9), we found the conditions of entry 10 best to give dihydroisoquinoline **14** in 60% yield. Under these conditions, the product yields of various sulfonyl derivatives fall in the following order: **15** (R = Et, entry 11) > **16** (R = *n*-Bu, entry 12) > **14** (R = Me, entry 10) > **17** (R = *i*-Pr, entry 13). Thus, alkyl substituent (R) of sulfonyl group had certain influence on the product yields, and among bromoolefins **9**, **11**, **12**, and **13**, ethanesulfonyl derivative **9** showed the highest yield (73%, entry 11). The size of sulfonyl groups may control the proximity of the phenyl and bromoolefin moieties suitable for the cyclization. Finally, further improvement of the yield could be achieved with ethanesulfonamide derivative **9** by increasing the amount of KOAc from 2 to 3 equiv, giving desired **15** in 80% yield (entry 14). Decreasing the amount of $Pd(OAc)_2$ from 10 to 8 or 5 mol% retarded the reaction so that starting bromolefin **9** remained even after prolonged reaction periods (2 or 8 h in entries 15 or 16, respectively).

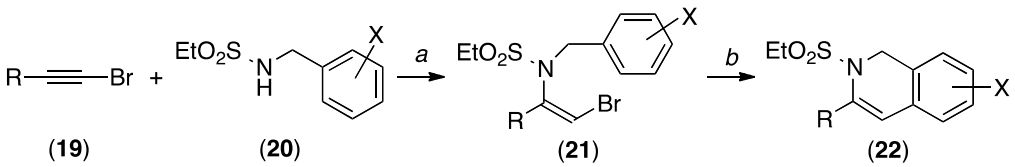
The dihydroisoquinoline structure assigned to **15** was confirmed by its derivatization to known isoquinoline **18**[12] via elimination of the sulfonyl group with *t*-BuOK as shown in eq 1.



(**15**) (**18**) 91% (1)

Table 3 shows other 1,2-dihydroisoquinolines prepared from various 1-bromo-1-alkynes and *N*-benzylsulfonamides. Entries 1-6 show the variation of aryl groups in *N*-benzylsulfonamides, where the sulfonamides having an electron-rich (**27** and **28** in entries 2 and 3) or electron-deficient (**29** in entry 4) aryl group gave *cis*-olefinic adducts **32**-**34** in good yields. These products, in turn, underwent the cyclization via C-H bond activation under Pd catalysis to furnish dihydroisoquinolines **41**-**43** again in good yields. Even when the starting sulfonamides have a sterically demanding benzyl group (**30** and **31** in entries 5 and 6), both nucleophilic addition and cyclization proceeded without any difficulty to afford the desired products **44** and **45** in comparable yields via the intermediate *cis*-bromoolefins **35** and **36**. This preparation shows reasonable generality also for 1-bromo-1-alkynes. For example, they can carry an ω-benzyloxy or propargylic methoxy group in their alkyl side chains (**23** and **24**, entries 7 and 8) to give adducts **37** or **38** and then the corresponding 1,2-dihydroisoquinolines **46** or **47** in satisfactory yields. It should be noted that a free terminal or propargylic hydroxy group in the side chain of bromoacetylenes **25** and **26** (entries 9 and 10) does not need protection and it survived whole reaction conditions to give 1,2-dihydroisoquinolines **48** and **49** in good overall yields.

Table 3. Preparation of various 1,2-dihydroisoquinolines

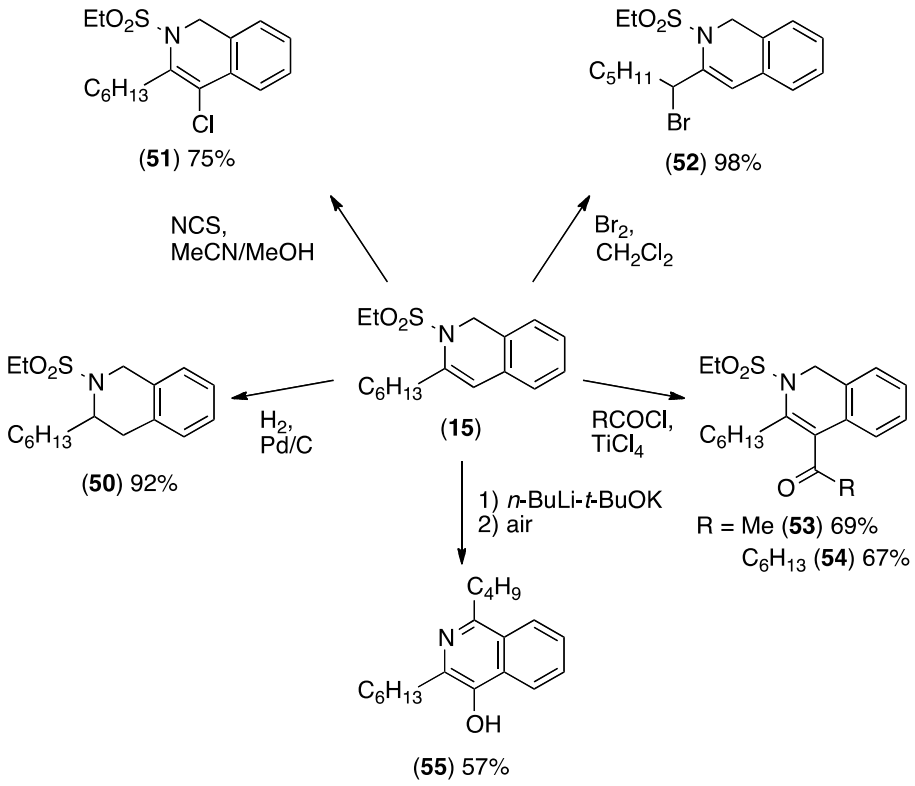


(**19**) (**20**) (**21**) (**22**)

Entry	R in **19**	XC_6H_4- in **20**	Product **21** Yield (%)[c]	Product **22** Yield (%)[d]
1	C_6H_{13}- (**2**)	Ph (**4**)	(**9**) 69	(**15**) 80
2	C_6H_{13}- (**2**)	4-MeC_6H_4- (**27**)	(**32**) 72	(**41**) 79
3	C_6H_{13}- (**2**)	4-$MeOC_6H_4$- (**28**)	(**33**) 63	(**42**) 78
4	C_6H_{13}- (**2**)	4-ClC_6H_4- (**29**)	(**34**) 66	(**43**) 86
5	C_6H_{13}- (**2**)	2-MeC_6H_4- (**30**)	(**35**) 62	(**44**) 79
6	C_6H_{13}- (**2**)	3,5-$Me_2C_6H_3$- (**31**)	(**36**) 65	(**45**) 78
7	BnO (**23**)	Ph (**4**)	(**37**) 66	(**46**) 79
8	OMe (**24**)	Ph (**4**)	(**38**) 50	(**47**) 84
9	HO$)_5$ (**25**)	Ph (**4**)	(**39**) 67	(**48**) 80
10	OH (**26**)	Ph (**4**)	(**40**) 61	(**49**) 88

[a]The reaction was carried out according to entry 2 of Table 1. [b]The reaction was carried out according to entry 14 of Table 2. [c]Isolated yield based on **19**. [d]Isolated yield from **21**.

In order to show synthetic utility of the products, we performed several transformations starting from representative dihydroisoquinoline **15** (Scheme 2). First, **15** was readily hydrogenated to tetrahydroisoquinoline **50** in 92% yield under 1 atm of H_2. While the chlorination of **15** with *N*-chlorosuccinimide proceeded at its enamine moiety to give 4-chloro-1,2-dihydroisoquinoline **51**,[13] its bromination with Br_2 unexpectedly took place at the allylic position to furnish **52** having a bromoalkyl side chain.[14,15] On the other hand, the $TiCl_4$-promoted Friedel-Crafts reaction of **15** with alkanoyl chlorides gave 4-alkanoyl-1,2-dihydroisoquinolines **53**[16] and **54** in good yields. When **15** was treated with *n*-BuLi-*t*-BuOK,[17] the intermediary formation of **18** (see eq 1) was followed by the addition of butylmetal species at its 1-position to give metalloenamine, which was then oxidized with air to give 1-butyl-4-hydroxyisoquinoline **55**, consistent with a precedent in the literature.[18]



Scheme 2. Transformations from 1,2-dihydroisoquinoline **15**

In conclusion, *N*-benzylsulfonamides underwent the nucleophilic addition to 1-bromo-1-alkynes in a highly regio- and stereoselective manner to give *cis*-bromoolefins in good yields. Their subsequent Pd-catalyzed cyclization via aromatic C-H bond activation gave 1,2-dihydroisoquinolines in good yields. Some synthetic applications of these 1,2-dihydroisoquinolines are also illustrated.

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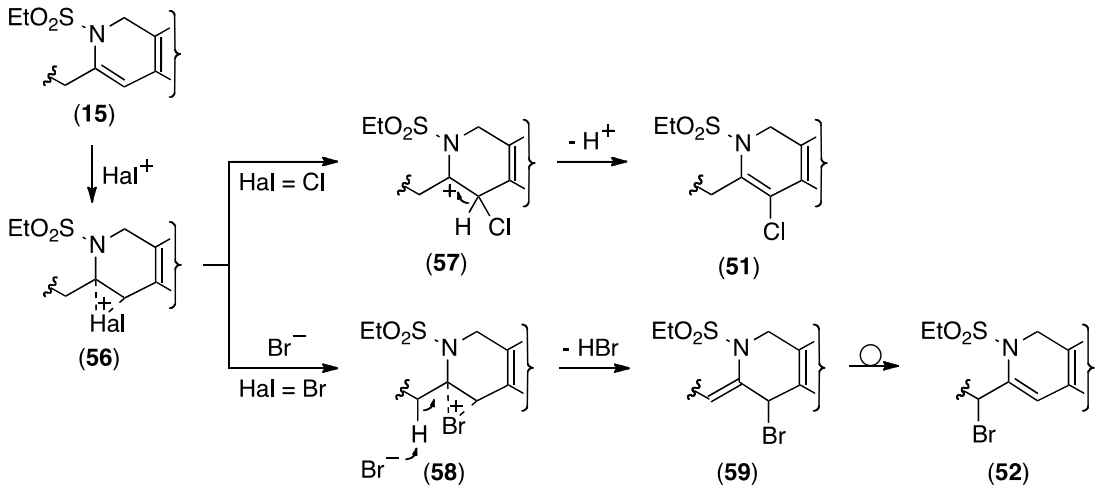
13. In a crude reaction mixture, the chloro derivative of **52** was also detected as a minor component (**51**/Cl-**52** = 90:10). For details, see Supporting Information.

14. The selection between **51** and **52** does not arise from the reaction conditions, because from **15** and *N*-bromosuccinimide under the same reaction conditions of the chlorination, **52** was again produced in 70% yield. Alternatively, the reaction of **15** with Br_2 in the dark did not block the formation of **52**, negating the light-induced allylic bromination. Thus, the reactive chloronium ion **56** (Hal = Cl) may collapse to cation intermediate **57**, which release a proton to give vinyl chloride **51**. However, less reactive bromonium ion **56** (Hal = Br) needs the nucleophile-assisted deprotonation (**58**) to give allylic bromide **59**, which spontaneously isomerized to more stable **52**.



15. Halogenated heterocycles (including even chlorinated ones) are versatile synthetic intermediates: (a) J. J. Li and G. W. Gribble, 'Palladium in Heterocyclic Chemistry,' Pergamon Press, Inc., Amsterdam, 2000; (b) T. Liu and H. Fu, *Synthesis*, 2012, **44**, 2805; (c) H. Li, C. C. C. Johansson Seechurn, and T. J. Colacot, *ACS Catal*., 2012, **2**, 1147; (d) S. M. Wong, C. M. So, and F. Y. Kwong, *Synlett*, 2012, **23**, 1132; (e) S. L. Buchwald, *Acc. Chem. Res*., 2008, **41**, 1439; (f) E. A. B. Kantchev, C. J. O'Brien, and M. G. Organ, *Angew. Chem. Int. Ed*., 2007, **46**, 2768; (g) R. J.

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16. After the titanium-promoted acylation, α,β-unsaturated ketone **53** was obtained as a mixture of itself and the corresponding β,γ-unsaturated isomer, which readily isomerized to single **53** with DBU in 69% overall yield from **15**. For details, see Supporting Information.
17. The use of *n*-BuLi without *t*-BuOK gave only a trace amount of **55**. For a recent example on the use of *n*-BuLi-*t*-BuOK, see: C. Unkelbach, H. S. Rosenbaum, and C. Strohmann, *Chem. Commun*., 2012, **48**, 10612.
18. H. Uno, S. Okada, and H. Suzuki, *J. Heterocycl. Chem*., 1991, **28**, 341.