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Cyclic Amination onto Aromatic Ring of Sulfonamides with (Diacetoxyiodo)arenes: Effect of Sulfonyl Group

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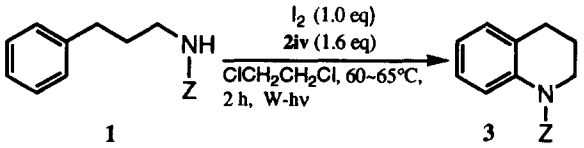
Abstract: Sulfonamides of primary amine bearing an aromatic ring at γ-position were treated with (diacetoxyiodo)arene and iodine under irradiation conditions with a tungsten lamp to give the corresponding 1,2,3,4-tetrahydroquinoline derivatives in moderate to good yields. The present reaction proceeded under mild and neutral conditions. Copyright © 1996 Elsevier Science Ltd

Many natural products contain six- or five-membered heterocyclic rings bearing nitrogen atoms. 1,2,3,4-Tetrahydroquinoline skeletons are of particular interest, because of their importance in the total synthesis of natural products as well as in medicinal chemistry.[1] Therefore, extensive studies on the preparation of these skeletons have been carried out, mainly with condensation and cycloaddition methods.[2] Among these preparations, the method with radical reactions is very useful,[3] since it is mechanistically unusual. However, study on the radical cyclization onto the aromatic ring via an aminyl radical is extremely limited, *i.e.*, the formation of an aminium radical generated by the photolytic or ferrous ion-catalyzed decomposition of N-chloroamines in strong acidic media,[4] and the yields in these reactions are less than satisfactory.

Here, as a part of our study on the reactivity of (diacetoxyiodo)arenes as radical precursors,[5] we report a good preparation method of six-membered cyclic aromatic amine from primary amine bearing an aromatic ring at γ-position that is easily operable under neutral conditions, through the radical amination onto the aromatic ring. Hitherto, the Hofmann-Löffler-Freytag type reaction of nitroamines and cyanoamides derived from steroidal compounds, with (diacetoxyiodo)benzene and iodosobenzene has been studied by Suárez *et al.*[6] However, the cyclic amination onto aromatics has been never studied. At first, when the amides protected by trifluoroacetyl (**1a**), *p*-methylbenzoyl (**1b**), ethoxycarbonyl, and ethyl oxalyl were warmed at 60~65°C in the presence of (diacetoxyiodo)benzene and iodine under irradiation with a tungsten lamp (500 W), the cyclization onto the aromatic ring did not occur at all and the starting amides were recovered. However, when the sulfonamides were treated with (diacetoxyiodo)benzene and iodine under the same conditions, the corresponding cyclization products, 1,2,3,4-tetrahydroquinoline derivatives, were obtained in moderate to good yields.[7] The results are shown in Table 1. Here, the electron-withdrawing substituent on the aromatic ring of *p*-substituted benzenesulfonamides gave the cyclic products in good yields. Thus, the trifluoromethanesulfonyl group, the most powerful electron-withdrawing group, showed the best reactivity. The amide protected by diethyl phosphate did not give the cyclized product

Table 1. Relationship Between Chemical Shift of Starting Sulfonamides (1) and Yields

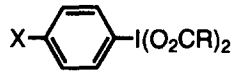


1 3

Entry	(1) Z	^{13}C-NMR[a] δ (NH-$\underline{C}H_2$) ppm	Yield / %
1	$OCCF_3$ (a)	39.58	0[b]
2	OC-C6H4-CH_3 (b)	39.70	0[b]
3	$PO(OC_2H_5)_2$ (c)	40.85	0
4	O_2S-C6H4-OCH_3 (d)	42.51	15
5	O_2S-C6H4-CH_3 (e)	42.56	48
6	O_2S-C6H4- (f)	42.58	59
7	O_2S-C6H4-NO_2 (g)	42.69	67
8	O_2SCF_3 (h)	43.93	71

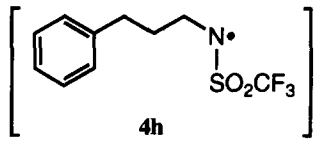
a) $CDCl_3$-TMS. b) Starting amide was recovered in >80% yield.

Table 2. Substituent Effect of (Diacyloxyiodo)-arenes in the Reaction with Compound **1g**



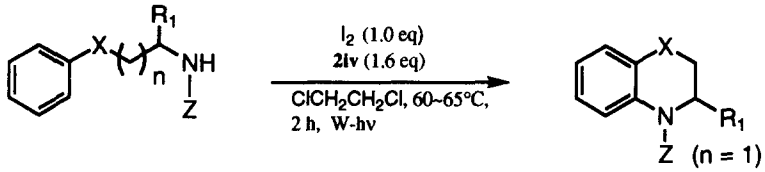
2

	3, Yield / %
2i : X = H, R = CF_3	0
2ii : X = NO_2, R = CH_3	71
2iii : X = Cl, R = CH_3	66
2iv : X = H, R = CH_3	67
2v : X = CH_3, R = CH_3	65
2vi : X = CH_3O, R = CH_3	61
2vii: X = H, R = CH_2CH_3	64



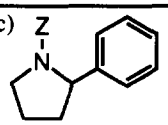
4h

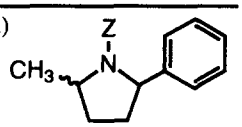
Table 3. Conversion of Various Sulfonamides to Cyclic Sulfonamides



Entry	n	X	R_1	Z	Yield / %
1	1	$CHCH_3$	H	(h)	80
2		O	H	(h)	72[a]
3		CH_2	CH_3	(h)	41
4		CH_2	C_4H_9	(h)	13[b]
5		CH_2	Ph	(h)	43
6	2	CH_2	H	(g)	84[c]
7		CH_2	CH_3	(g)	71[d]

a) 6-Iodo compound was also formed in ~9% yield. b) I_2 (1.5 eq) and **2iv** (2.4 eq).

c) 

d) 

(cis:trans = 35:65)

(entry 3). The relationship between the ^{13}C-NMR chemical shift of $NHCH_2$ group in the starting compound **1** and the yield of the cyclized product **2** was observed, though the difference is small. Thus, the reaction requires a lower field chemical shift than 42 ppm in compound **1**. This reactivity probably depends on the acidity of sulfonamides and the stability of sulfonamidyl radicals. Practically, there is ~10 order difference in pKa values of the NH proton between sulfonamides and amides.[8] The detailed reaction mechanism is still not completely clear. However, the present reaction did not proceed at all without irradiation with a tungsten lamp or without (diacetoxyiodo)benzene. Thus, N-I bond formation species of compound **1** is the one of the reactive intermediates and its homolytic cleavage occurs to give the sulfonamidyl radical such as **4h** under the irradiation conditions.

Next, the substituent effect of the aromatic ring in (diacetoxyiodo)arene was studied under the same conditions as shown in Table 2. However, no big difference between the nitro and methoxy groups was observed. [Bis(trifluoroacetoxy)iodo]pentafluorobenzene and [bis(trifluoroacetoxy)iodo]benzene (**2i**) did not give the compound **3**.

Thus, the other sulfonamides were treated with (diacetoxyiodo)benzene and iodine under the same conditions. The results are shown in Table 3. The sulfonamides derived from primary and secondary alkyl branched amines were converted to the corresponding sulfonamides of the cyclic aromatic amines in moderate yields. On the other hand, the sulfonamides bearing an aromatic group at δ-position gave the pyrrolidine derivatives bearing an aromatic ring at α-position via the Hofmann-Löffler-Freytag type reaction (entries 6 and 7).[9] This is very interesting, because the present reaction can be applicable to the preparation of aza-nucleosides.[10]

The present method is very useful for the preparation of six-membered cyclic aromatic amine, because the reaction proceeds by a simple operation, and under mild and neutral conditions. The last reaction, the Hofmann-Löffler-Freytag type reaction, may be also useful as a new preparation method of aza-C-nucleosides, because past methods are limited to the coupling reaction of azasugars and metallated aryl species. Study on further extension is now under way.

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7. *General procedure is as follows*: To a solution of sulfonamide (0.5 mmol) in 1,2-dichloroethane (7 ml) were added (diacetoxyiodo)benzene (0.8 mmol) and iodine (0.5 mmol). The mixture was irradiated at 60~65°C with a tungsten lamp (500 W) for 2 h under argon atmosphere. After the reaction, the mixture was poured into chloroform and washed with aq. sodium sulfite solution and subsequently with water. The organic layer was dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel by pTLC to give the product.
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