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# A FACILE METHOD FOR CONVERSION OF PHENOLIC TETRAHYDROISOQUINOLINES TO BENZYLAMINES WITH RING CLEAVAGE

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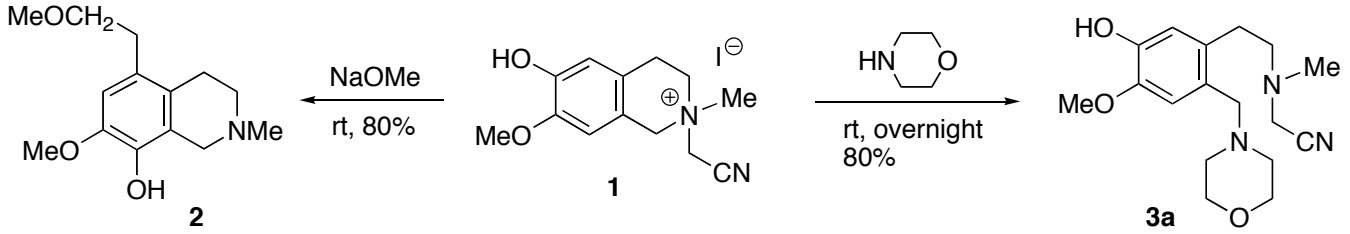
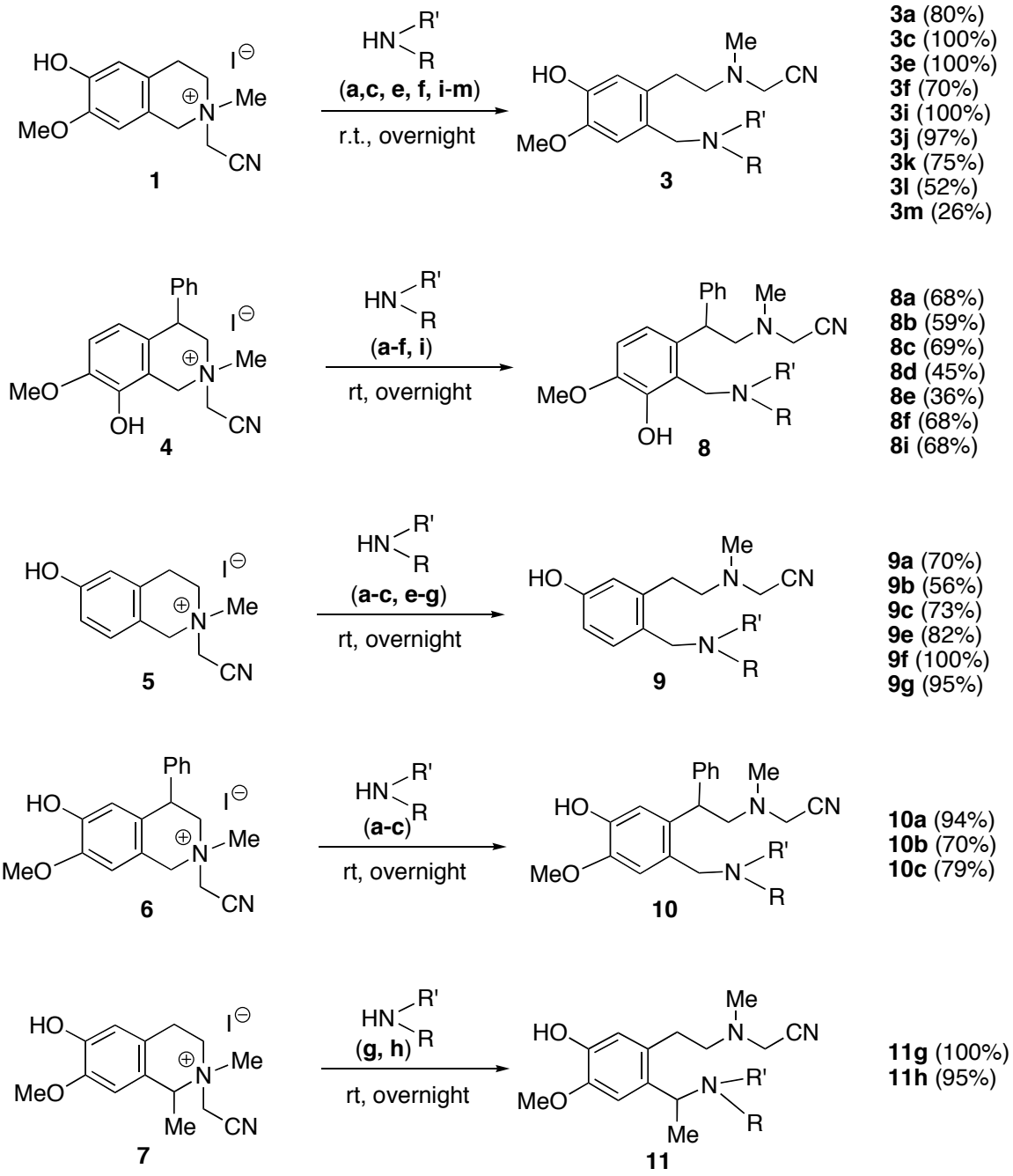
**Abstract** – The reaction of *N*-cyanomethyl-6- and -8-hydroxytetrahydroiso-quinolinium methiodide with various amines afforded the corresponding benzylamines *via* the formation of *p*- or *o*-quinone methide in moderate to high yields.

Synthetic methods of many kinds of isoquinoline alkaloids have already been established.[1] Therefore, the transformation of tetrahydroisoquinolines into other skeletons is quite valuable from the point of view of useful sources of naturally occurring tetrahydroisoquinolines[2] and the search for biological compounds. During the work according to this concept, we have reported the NaOMe-mediated new rearrangement of *N*-(cyanomethyl)isoquinolinium methiodide (**1**), which could be prepared from tetrahydroisoquinolines with iodoacetonitrile, to give tetrahydroisoquinolin-8-ol (**2**) in high yield (Scheme 1).[3,4] When we investigated the reaction of **1** using other bases, we found that the reaction of **1** with morpholine furnished a benzylamine (**3a**) with ring cleavage of **1**. Thus, the present reaction seems to be a facile transformation of phenolic tetrahydroisoquinolenes to the corresponding benzylamines. We wish to describe our investigation on the present transformation using various amines.

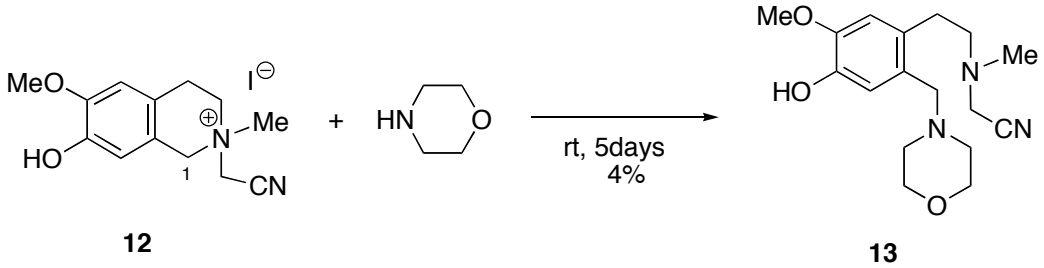



**Scheme 1**


HO
MeO
I⊖
Me
CN
1
HN R'
R
(a,c, e, f, i-m)
r.t., overnight
Me
N
CN
R'
R
3
3a (80%)
3c (100%)
3e (100%)
3f (70%)
3i (100%)
3j (97%)
3k (75%)
3l (52%)
3m (26%)
Ph
OH
4
(a-f, i)
rt, overnight
8
8a (68%)
8b (59%)
8c (69%)
8d (45%)
8e (36%)
8f (68%)
8i (68%)
5
(a-c, e-g)
rt, overnight
9
9a (70%)
9b (56%)
9c (73%)
9e (82%)
9f (100%)
9g (95%)
6
(a-c)
rt, overnight
10
10a (94%)
10b (70%)
10c (79%)
7
Me
(g, h)
rt, overnight
11
11g (100%)
11h (95%)
a
b
c
d
e
f
g
4-FC6H4
h
i
j
k
l
m

**Scheme 2**

At first, the reaction of *N*-(cyanomethyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-isoquinolinium iodide (**1**) was examined. The reaction of **1** with various primary and secondary amines gave the expected benzylamines (**3**)[5] in good to high yields except for the reaction with 1-adamantylamine probably due to a steric reason (Scheme 2). To investigate the scope and limitation of the present reaction, a similar reaction of other substrates (**4**-**7**)[3] was carried out. The reaction of an 8-hydroxy derivative (**4**) with various amines afforded the products (**8**)[5] in moderate to good yields. A substrate (**5**)[3] bearing no methoxy group at the C7 position and isoquinolinols (**6**, **7**),[3] which have a substituent at the C1 or C4 position, also accepted the reaction to afford the corresponding benzylamines (**9**-**11**).[5] It is noteworthy that the ether, sulfide, *tert*-amine, and alcohol moieties did not affect the present reaction. On the other hand, a similar reaction of **12**[3] with morpholine was very sluggish and the expected benzylamine (**13**)[5] was obtained in only 4% yield (Scheme 3).

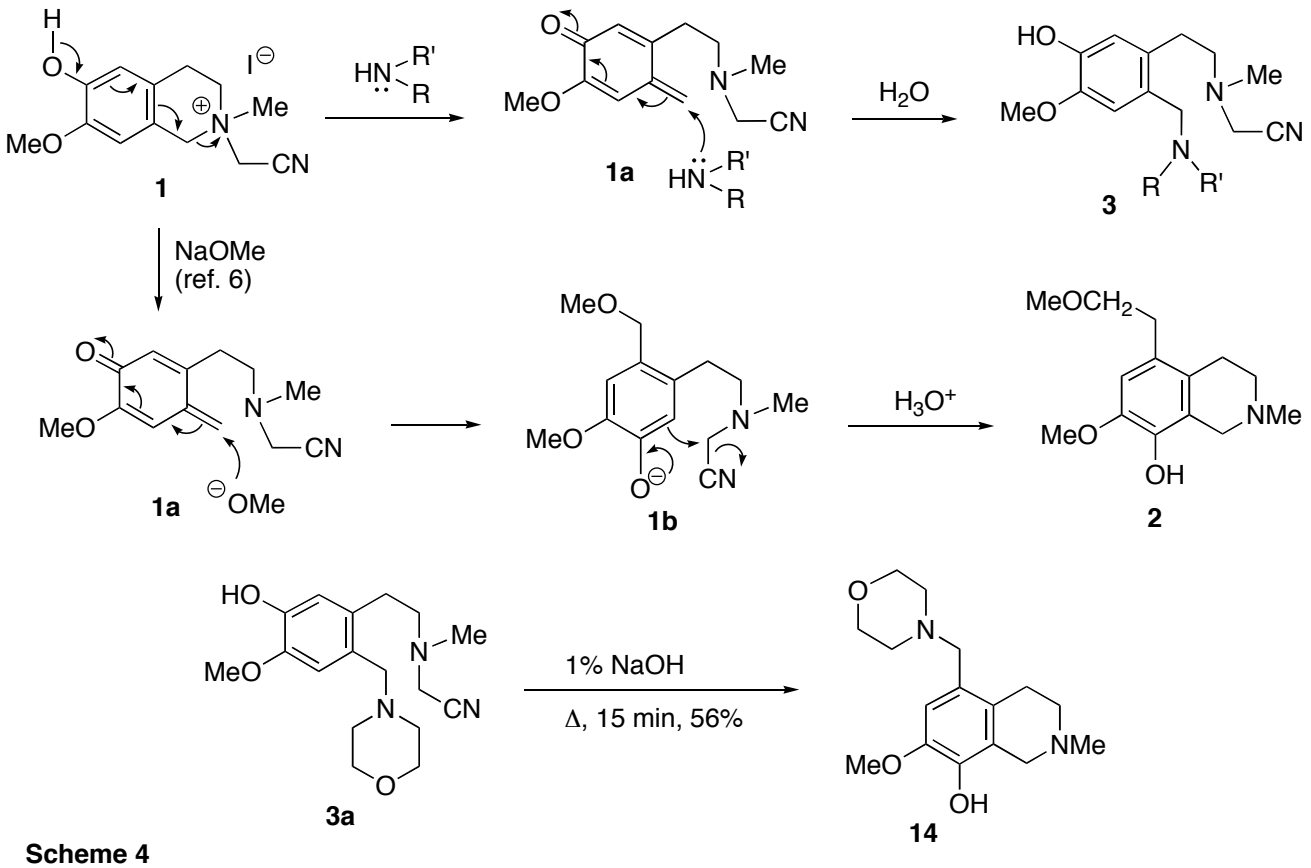



**12** **13**

**Scheme 3**

These results are consistent with the plausible mechanism, as shown in Scheme 4. Thus, an amine abstracts a phenolic hydrogen of **1** similar to the reported mechanism of **1** with NaOMe[6] to produce an *p*-quinone methide (**1a**). Subsequent conjugate addition of the amine to **1a** furnished the corresponding benzylamine (**3**). A similar reaction of the 8-hydroxy derivative (**4**) would proceed *via* the formation of the *o*-quinone methide. Because the substrate (**12**), which has a hydroxy group at the C7-position, could not generate such a quinone methide, **13** would be formed by the direct $S_N2$ type reaction at the C1 position of **12**. Moreover, since an amine is a weak base compared to NaOMe, cyclization of the benzylamine (**3**) to tetrahydroisoquinoline did not occur. This assumption was confirmed by the reaction of benzylamine (**3a**) with 1% NaOH to produce the tetrahydroisoquinolinol (**14**) in 56% yield by cyclization at the *o*-position of the hydroxy group of **3a**.

In conclusion, we have investigated the reaction of various *N*-(cyanomethyl)isoquinolinium methiodides (**1**, **4**-**7**, **12**) with various amines. The present reaction provides a new method for a simple conversion of 6- or 8-hydroxytetrahydroisoquinolines to the corresponding benzylamines, which may have potential as candidates for drugs, because of their plural favorable groups for interaction with enzymes and receptors.




**Scheme 4**

## ACKNOWLEDGEMENTS

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