

HETEROCYCLES, Vol. 65, No. 9, 2005, pp. 2057 - 2060

Received, 26th May, 2005, Accepted, 11th July, 2005, Published online, 12th July, 2005

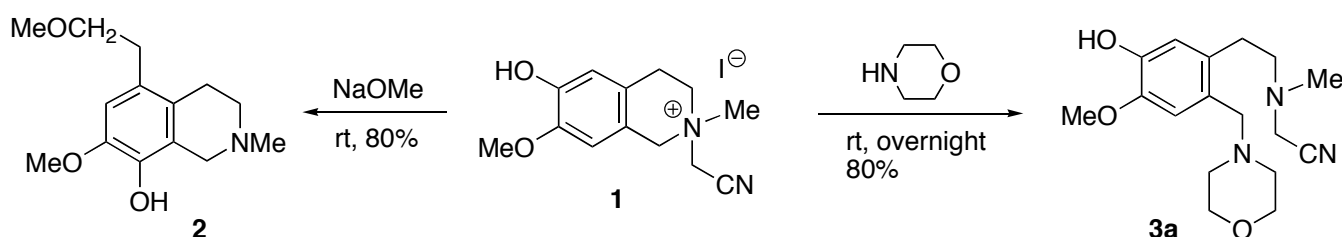
A FACILE METHOD FOR CONVERSION OF PHENOLIC TETRAHYDROISOQUINOLINES TO BENZYLAMINES WITH RING CLEAVAGE

Takashi Nakata, Naho Komatsu, Mamiko Yamanaka, Hae Joo Lee, Yutaka Matsuoka, Kiyoshi Nishitani, Miyuki Ishizaki, and Hiroshi Hara*

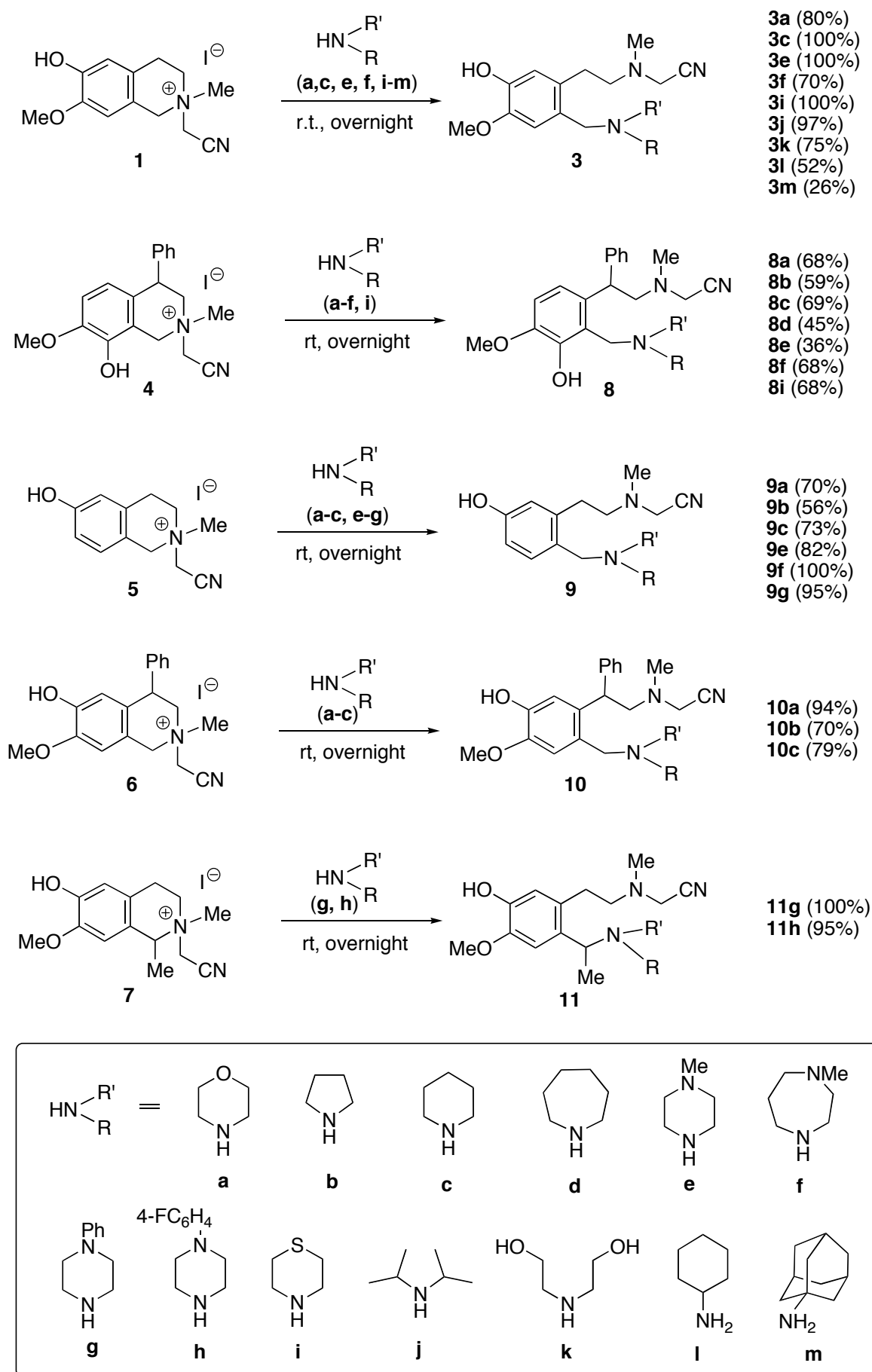
Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641, Yamazaki, Noda-shi, Chiba 278-8510, Japan

Abstract – The reaction of *N*-cyanomethyl-6- and -8-hydroxytetrahydroisoquinolinium 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 tetrahydroisoquinolines² 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 tetrahydroisoquinolines to the corresponding benzylamines. We wish to describe our investigation on the present transformation using various amines.

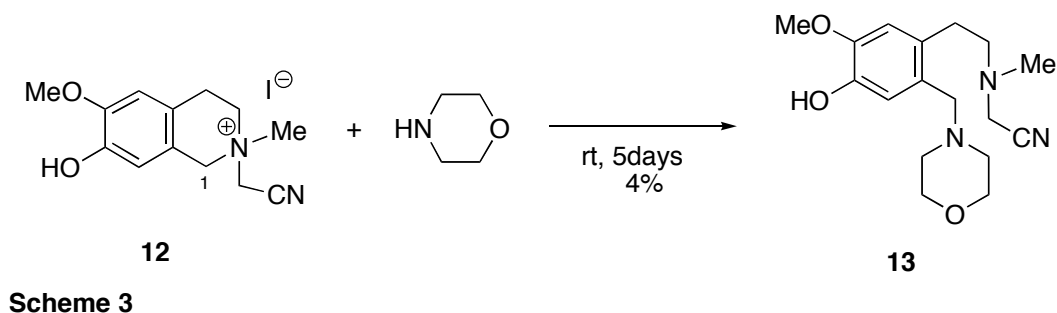


Scheme 1



Scheme 2

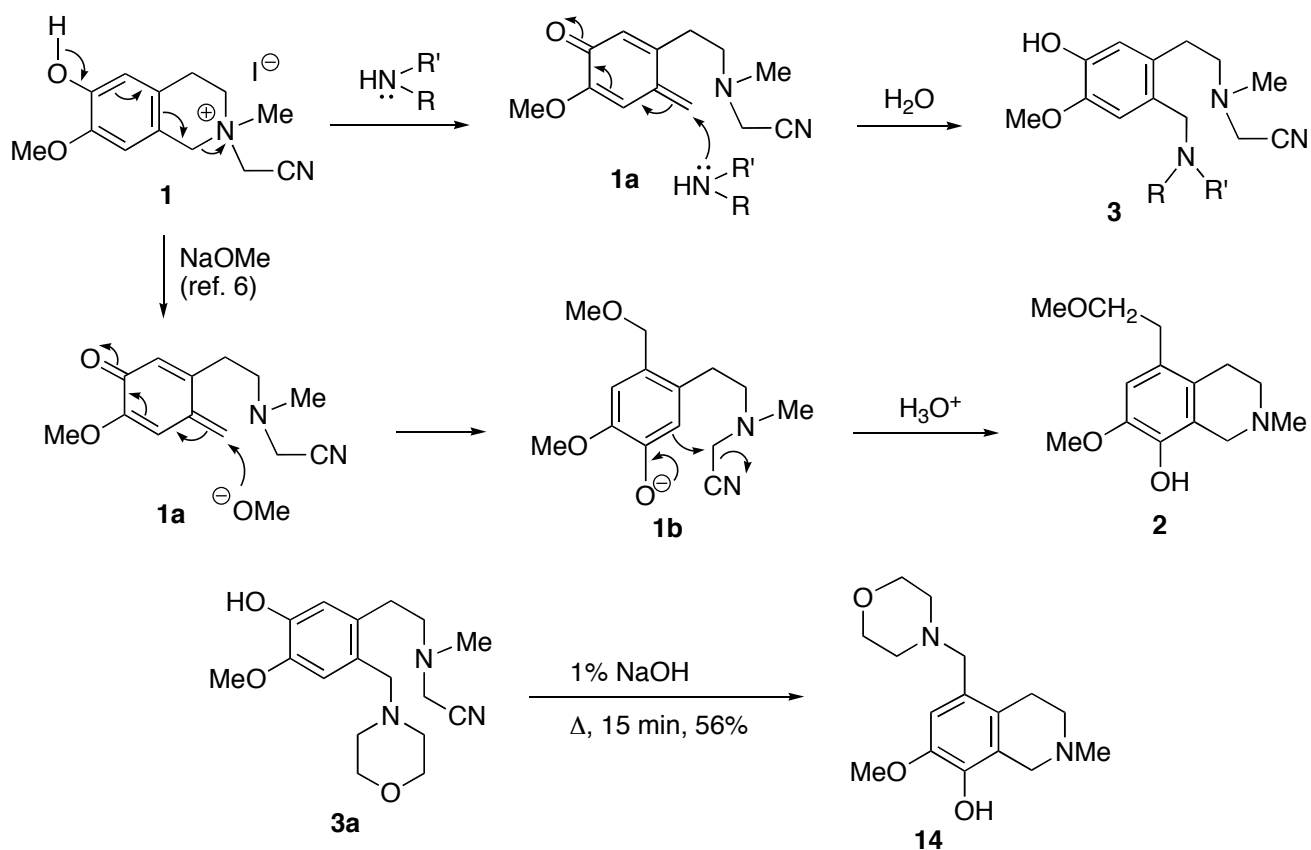
At first, the reaction of *N*-(cyanomethyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-isoquinolinium iodide (**1**) was examined. The reaction of **1** with various primary and secondary amines gave the expected benzylamines (**3**)⁵ in good to high yields except for the reaction with 1-adamantylamine probably 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).



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 NaOMe⁶ 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

The authors are grateful to Mrs. F. Hasegawa of this faculty for her MS spectral measurements.

REFERENCES AND NOTES

- Reviews for the synthesis of tetrahydroisoquinolines; (a) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341. (b) E. Anakabe, D. Badia, L. Carrillo, and J. L. Vicario, *Recent Research Developments in Organic Chemistry*, 2001, **5**, 63.
- K. W. Bentley, *Isoquinoline Alkaloids (Chemistry and Biochemistry of Organic Natural Products)*, 1998, T&F STM.
- H. Hara, M. Endoh, K. Kaneko, and O. Hoshino, *Heterocycles*, 1993, **36**, 249.
- For previous reports on the rearrangement of tetrahydroisoquinolines; (a) N. Kawanishi, N. Shirai, Y. Sato, K. Hatano, and Y. Kurono, *J. Org. Chem.*, 1995, **60**, 4272. (b) T. S. Bailey, J. B. Bremner, and J. A. Carver, *Tetrahedron Lett.*, 1993, **34**, 3331. (c) S. Jr. Smith, V. Elango, and M. Shamma, *J. Org. Chem.*, 1984, **49**, 581. (d) H. W. Bersch, R. Rissmann, and D. Schon, *Archiv Pharm.*, 1982, **315**, 749. (e) J. B. Bremner, E. J. Browne, P. E. Davies, and T. L. Van, *Aust. J. Chem.*, 1980, **33**, 833.
- All new compounds gave satisfactory ^1H -NMR, IR, and MS spectral data.
- H. Hara, K. Kaneko, M. Endoh, H. Uchida, and O. Hoshino, *Tetrahedron*, 1995, **51**, 10189.