RING TRANSFORMATIONS OF HETEROCYCLES VIA YLIDE INTERMEDIATES: SYNTHESIS OF HEXAHYDRO-2,3-DIAZEPINO[5,4-*b*]INDOLES FROM TETRAHYDRO-γ-CARBOLINES*

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Abstract —— *N*-Amination of 2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles with *O*-(*p*-toluenesulfonyl)-*N*-alkylhydroxylamines followed by base treatment gave the ring expanded products, 1,2,3,4,5,6-hexahydro-2,3-diazepino[5,4-*b*]indoles.

Although the chemistry of ammonium *N*-imines has recently received considerable attention, there are only a few examples of their use for the synthesis of heterocycles.[1] In connection with our interests in the ring transformations of heterocycles through ylide intermediates,[2] we wish to report a novel ring expansion reaction of the *N*-imines derived from 2-alkyltetrahydro-γ-carbolines (2-alkyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles) to 1,2,3,4,5,6-hexahydro-2,3-diazepino[5,4-*b*]indoles.

When (1a) was treated with *O*-(*p*-toluenesulfonyl)-*N*-methylhydroxylamine (2a)[3] in methylene chloride at room temperature for 2 h, the *N*-methylamine salt (3a), mp 170-171°C, was obtained in nearly quantitative yield. Refluxing (3a) in ethanol in the presence of potassium carbonate for 2 h gave (6a), mp 174-175°C, in quantitative yield. The structure of (6a) was based on the spectral evidence. The elemental analysis and mass spectrum (M^+, *m/e* 215) confirmed the molecular formula $C_{13}H_{17}N_3$. Its NMR spectrum ($CDCl_3$) revealed two *N*-methyl singlets at δ 2.44 and 2.57, a multiplet between δ 2.8-3.3 (4H, H-4 and -5), a singlet at δ 4.12 (2H, H-1), a multiplet (4H) in the aromatic region, and a broad singlet at δ 7.8 (1H, NH). Similarly (1b-d) were converted to (3b-d)[4] which, upon treatment with base,

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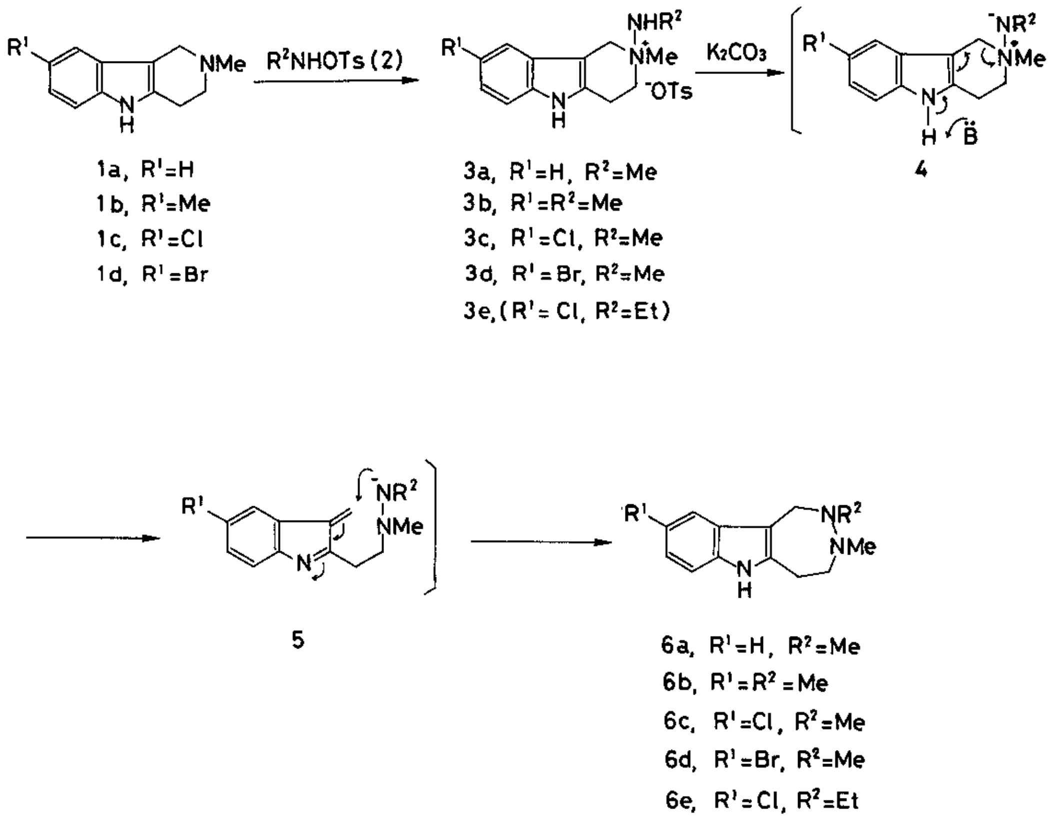
* Dedicated to Professor Kyosuke Tsuda on the occasion of his 75th birthday.

afforded (6b-d)[5] in good yields. By using *O*-(*p*-toluenesulfonyl)-*N*-ethylhydroxylamine (2b),[3] (1c) was transformed into (6e)[5] through (3e).[4]
This base-promoted ring expansion reaction may proceed *via* intermediates (5) formed by cleavage of the weak C-N bond of the initially formed *N*-imines (4). Intramolecular Michael type cyclization of (5) leads to (6).



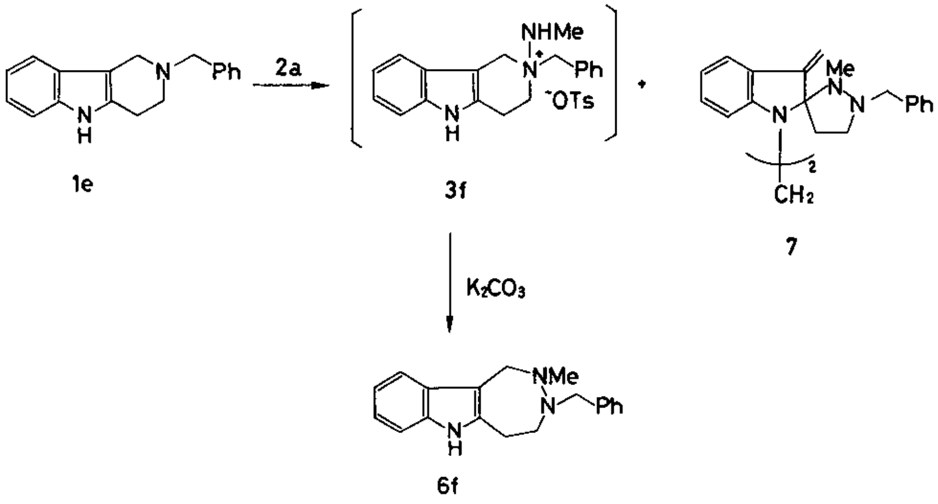
1a, R^1=H
1b, R^1=Me
1c, R^1=Cl
1d, R^1=Br

3a, R^1=H, R^2=Me
3b, R^1=R^2=Me
3c, R^1=Cl, R^2=Me
3d, R^1=Br, R^2=Me
3e, (R^1=Cl, R^2=Et)

6a, R^1=H, R^2=Me
6b, R^1=R^2=Me
6c, R^1=Cl, R^2=Me
6d, R^1=Br, R^2=Me
6e, R^1=Cl, R^2=Et

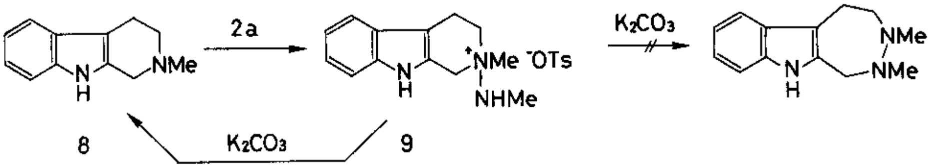
Scheme 1

When 2-benzyltetrahydro-γ-carboline (1e) was treated with (2a) in methylene chloride at room temperature for 5 h, a dark brown solution was obtained. Because an attempt to isolate (3f) in a pure form was unsuccessful, the solution was concentrated and the residue was heated in ethanol in the presence of potassium carbonate. After filtration and concentration of the filtrate, the crude material was chromatographed on silica gel to give a dimeric product (7) (1%), mp 205-206°C, in addition to the expected ring expanded product (6f) (54%), mp 144-145°C, and the starting material (1e) (27%). The yield of (7) increased to ca. 10% by standing a mixture of (1e) and (2a) in methylene chloride at room temperature for 16 h followed by refluxing the reaction mixture in ethanol for 2 h. The structure of (7) was assigned on the basis of spectral evidence. The elemental analysis and mass spectrum (M^+, 594) confirmed the molecular formula $C_{39}H_{42}N_6$. Its NMR spectrum showed the presence of two *N*-methyl groups [δ 1.93 (6H, s)], four methylene groups [δ 2.6-3.1 (8H, m)], two *N*-benzylic methylenes [δ 3.78 (4H, bs)], a methylene group [δ 4.07 (2H, s, NCH_2N)], two exocyclic methylene groups [δ 5.20 (4H, s)], and aromatic protons [δ 6.7-7.4 (18H, m)]. The precise mechanism for the formation of (7) is not clear at present.



Scheme 2

As a further extension of this reaction, we have applied to a tetrahydro-β-carboline (2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole) (8). Reaction of (8) with (2a) gave the *N*-methylamine salt (9) in 92% yield. However, base treatment of (9) resulted in the N-N bond cleavage to give (8).



Scheme 3

References and Notes

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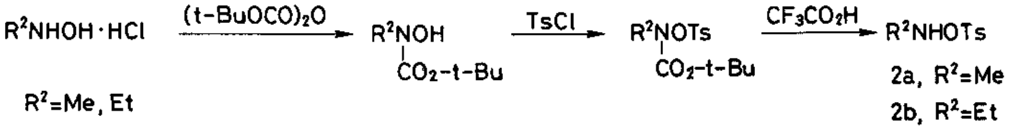
2 Y. Tamura, S.M. Bayomi, M. Ikeda, and M. Kise, *Chem. Pharm. Bull.* (Tokyo), 1980, **28**, 1597; Y. Tamura, S.M. Bayomi, C. Mukai, M. Ikeda, M. Murase, and M. Kise, *Tetrahedron Lett.*, 1980, **21**, 533; Y. Tamura, S.M. Bayomi, C. Mukai, M. Ikeda, and M. Kise, *J.C.S. Perkin I*, 1980, 2830; Y. Tamura, Y. Takebe, C. Mukai, and M. Ikeda, *Heterocycles*, 1981, **15**, 875; Y. Tamura, Y. Takebe, S.M. Bayomi, C, Mukai, M. Ikeda, M. Murase, and M. Kise, *J.C.S. Perkin I*, 1981, 1037.

3 This compound was prepared from the corresponding *N*-alkylhydroxylamine hydrochlorides by a route as shown in the following Scheme (Y. Tamura, H. Ikeda, I. Morita, H. Tsubouchi, and M. Ikeda, to be published).



$$\underset{R^2=Me,\,Et}{R^2NHOH\cdot HCl} \xrightarrow{(t\text{-}BuOCO)_2O} \underset{\displaystyle CO_2\text{-}t\text{-}Bu}{R^2\underset{|}{N}OH} \xrightarrow{TsCl} \underset{\displaystyle CO_2\text{-}t\text{-}Bu}{R^2\underset{|}{N}OTs} \xrightarrow{CF_3CO_2H} R^2NHOTs$$

2a, R^2=Me

2b, R^2=Et

4 Compound (3b) (94%): mp 171-172°C. Compound (3c) (74%): mp 174-176°C. Compound (3d) (73%): mp 175-176°C. Compound (3e) did not crystallize.

5 Compound (6b) (72%): mp 155-157°C. Compound (6c) (67%): mp 177-179°C. Compound (6d) (70%): mp 166-167°C. Compound (6e) [30% overall yield from (1c)]: mp 122-123°C.

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