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STERIC EFFECT ON THE FORMATION OF 3*H*-AZEPINE DERIVATIVES FROM *o*-ALKYLPHENYLNITRENE AND ALCOHOL AS A NUCLEOPHILIC MEDIA

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Abstract – The cause of regioselectivity for the formation of 3-alkyl- and/or 7-alkyl-3*H*-azepine derivatives *via* the intramolecular insertion reaction of *o*-alkylphenylnitrene, which is generated by an action of Bu_3P on *o*-alkylnitrobenzene, in the presence of alcohol found to be elucidated by the steric effects of an alcohol adduct on the dehydroazepine intermediate. Observed selectivity is confirmed both by changing the bulkiness of the *o*-alkyl group of phenylnitrene and that of alcohol as a nucleophile.

The behavior of a singlet phenylnitrene (**1**) has been studied theoretically[1] and/or experimentally,[2] that is, the intramoleculer insertion reaction of nitrogen atom leads to a labile benzoazirine **2** and subsequent ring opening reaction gives seven membered dehydroazepine **3**. Typical synthetic application of this reaction is the synthesis of 3*H*-azepine derivatives. When phenylnitrene is generated in the presence of nucleophilic media (NuH) such as alcohol and amine, 2-alkoxy- or 2-amino-3*H*-azepine derivatives are obtained in practical yields. Reaction mechanism is often explained as in Figure 1, includes two possible reaction paths (path A and path B) before giving the final 3*H*-azepine **6**. That is to say, nucleophile attacks on azirine **2** to give an aziridine **4** (path A) and thermally allowed ring opening occurs to form 1*H*-azepine **5** then isomerizes to stable 3*H*-azepine **6** by a rapid 1,3-prototropy.[3] On the other hand, azirine **2** isomerizes into dehydroazepine **3** which is trapped by NuH to give 1*H*-azepine **5** and subsequent isomerization gives 3*H*-azepine **6** (path B).[4,5] Thus far the reaction path giving 3*H*-azepine has not been clarified experimentally. We report here 2-alkoxy-3*H*-azepine is produced *via* path B based on the experimental results by modifying the substituent and solvent on the reaction of *o*-alkylphenylnitrene.

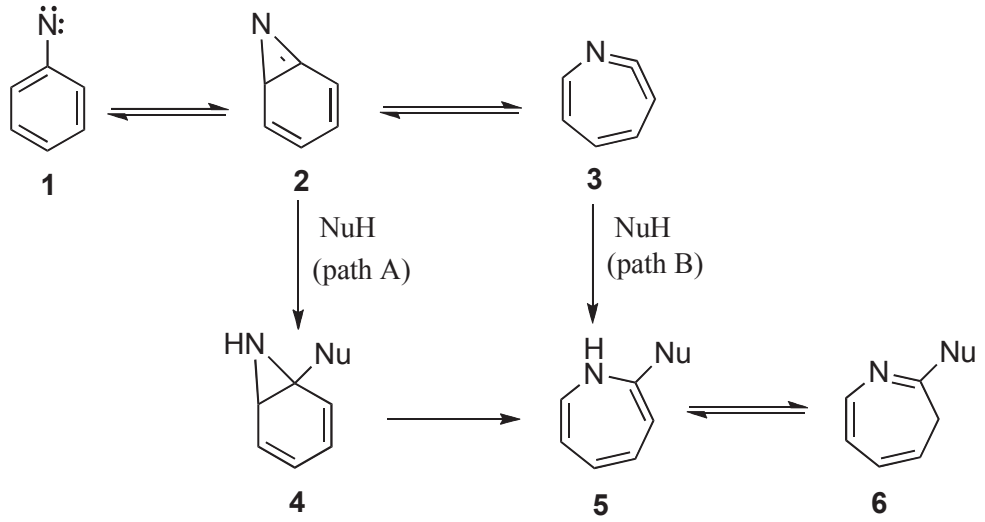
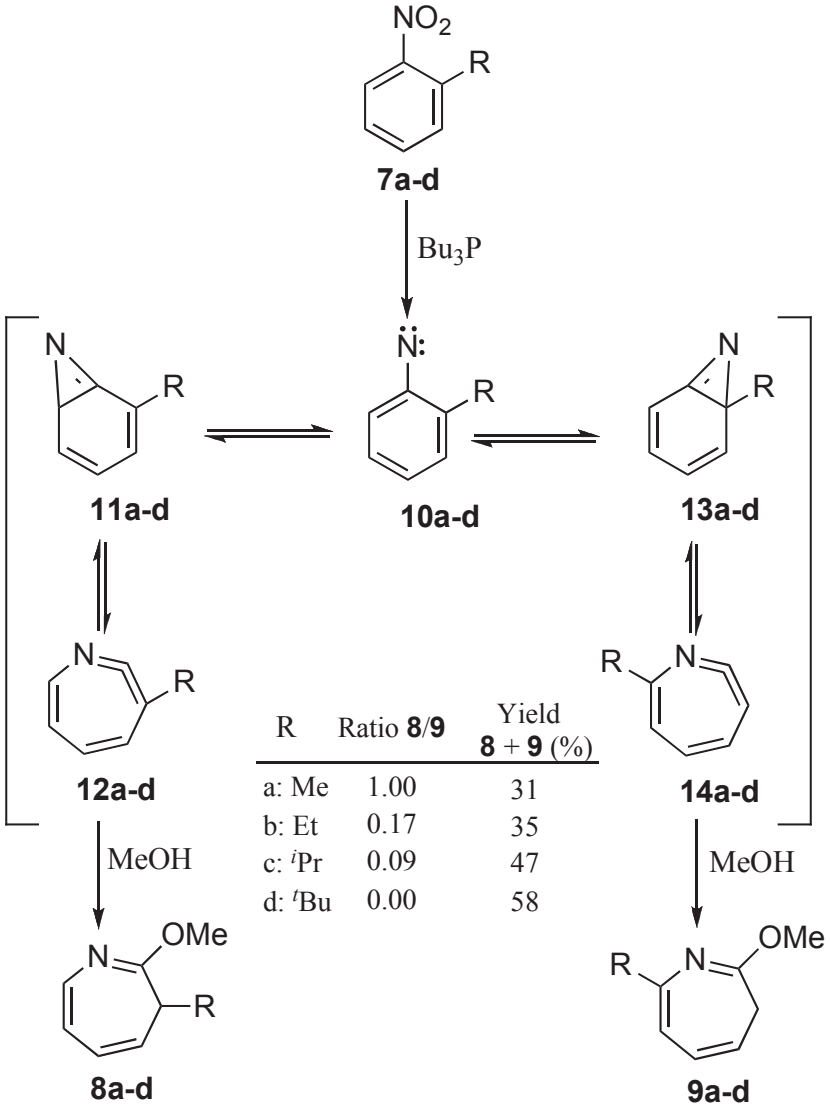


Figure 1. Plausible mechanism for the synthesis of 3*H*-azepine from phenylnitrene in the presence of nucleophile.

We have reported that the reaction of *o*-*tert*-butylnitrobenzene (**7d**) with Bu_3P under the presence of methanol (Scheme 1) resulted in the selective formation of 7-*tert*-butyl-2-methoxy-3*H*-azepine (**9d**) in 58% yield,[6] although, the formation of another isomeric product 3-*tert*-butyl-2-methoxy-3*H*-azepine (**8d**) can be expected as shown in Scheme 1. To elucidate this anomaly and to obtain the deeper insight into the mechanism of this reaction, we examined the reaction of several *o*-alkyl (methyl, ethyl and isopropyl) nitrobenzene derivatives (**7a**-**c**) with Bu_3P in methanol.

A representative procedure for the reaction of **7a**-**c** was as follows.[6,7] A solution of *o*-nitrotoluene (**7a**) (10 g, 73 mmol), 2 equiv. of Bu_3P and methanol (50 ml) was degassed for an hour with nitrogen flow then heated in a stainless sealed tube at 150 °C for 24 h. After cooling, the excess of solvent was removed and the resulted mixture was distilled under reduced pressure. The distillate was identified as a mixture of 3-methyl-3*H*-azepine **8a** and 7-methyl-3*H*-azepine **9a** by ^{1}H NMR analysis and determined the ratio between **8a** and **9a** by integration values. Chromatographic separation of the mixture using silica-gel column at 0 °C (AcOEt : hexane (1 : 19 v/v)) gave pure **8a** and **9a** without decomposition.[8] Similarly, reaction of *o*-ethylnitrobenzene (**7b**) and *o*-isopropylnitrobenzene (**7c**) also gave a mixture of 3-alkyl-3*H*-azepine **8b**,**c** and 7-alkyl-3*H*-azepines **9b**,**c** in respective ratio. The isomer **8a** and **9a** was appropriately characterized by ^{1}H NMR chemical shift. Olefinic four protons of **8a** were observed at $\delta_{H\text{-}4}$ 5.01, $\delta_{H\text{-}5}$ 6.16, $\delta_{H\text{-}6}$ 5.98, and $\delta_{H\text{-}7}$ 6.96 and three olefinic protons of **9a** were observed at $\delta_{H\text{-}4}$ 5.18, $\delta_{H\text{-}5}$ 6.13 and $\delta_{H\text{-}6}$ 5.86. Olefinic signal for **9a** suggest the lacking in the α-proton of nitrogen atom (H-7) which is expected for around 7 ppm, therefore, a methyl group is considered to be situated on C7-position on 3*H*-azepine **9a**.



R	Ratio **8**/**9**	Yield **8** + **9** (%)
a: Me	1.00	31
b: Et	0.17	35
c: ^{i}Pr	0.09	47
d: ^{t}Bu	0.00	58

Scheme 1

Since the *o*-substituted nitrobenzene **7** gave a mixture of **8** and **9**, possible intermediates **10** to **14** can be considered and illustrated on Scheme 1. The initially formed phenylnitrene **10** is cyclizes at either away or toward to *o*-substituent and give two kinds of benzoazirine intermediates **11** and **13**. Each of them is in equilibrium with dehydroazepine tautomer **12** and **14**. Subsequent addition of methanol to C=N bond of **11** and/or **12**gives 3-alkyl-3*H*-azepine **8** and that of **13** and/or **14**provides 7-alkyl-3*H*-azepine **9**.

The observed ratios of 3-alkyl isomer **8** to 7-alkyl isomer **9**, noted as **8**/**9**, in each reaction mixture are shown in Scheme 1. In the case of **7a** whereas the alkyl size is relatively small, the ratio **8a**/**9a** is 1.00, shows no selectivity in the formation of 3*H*-azepine, i.e. both sides reaction occurs almost even. In contrast, by modifying an *o*-alkyl group of **7** to the more bulky substituent, the ratio **8**/**9** decreases remarkably. When *o*-*tert*-butylnitrobenzene (**7d**) was employed as a starting material, exclusive formation of 7-*tert*-butyl isomer **9d** was obtained. This selectivity suggests that the precursor for 3*H*-azepine **9d** is azirine **13d** or dehydroazepine **14d** in the reaction of **10d**, i.e. the reaction proceeds only on right side of

Scheme 1. The product distribution gives us a clue to consider which path (see Figure 1, path A and B) is precedent to the final product. In the case of *o*-*tert*-butylphenylnitrene (**10d**), the possible structures of methanol adducts is considered to be methoxyaziridine **17** and methoxy-1*H*-azepine **18**, both of which will be 7-*tert*-butyl derivative **9d** (Figure 2). If this reaction proceeds *via* path A, it will includes the sterically unfavorable intermediate **17** because of vicinal steric hindrance between methoxy and bulky alkyl group on aziridine ring. In contrast, follows the path B, **14** can accept methanol without steric hindrance even though an alkyl group is bulky. Therefore, the favorable route to 3*H*-azepine should be considered as path B. In conformity with this view, small substituent as methyl group is allowable to attack intermediate **12** leads to **16** and finally give 3-methyl-3*H*-azepine **8a** in even ratio with 7-methyl-3*H*-azepine **9a**.

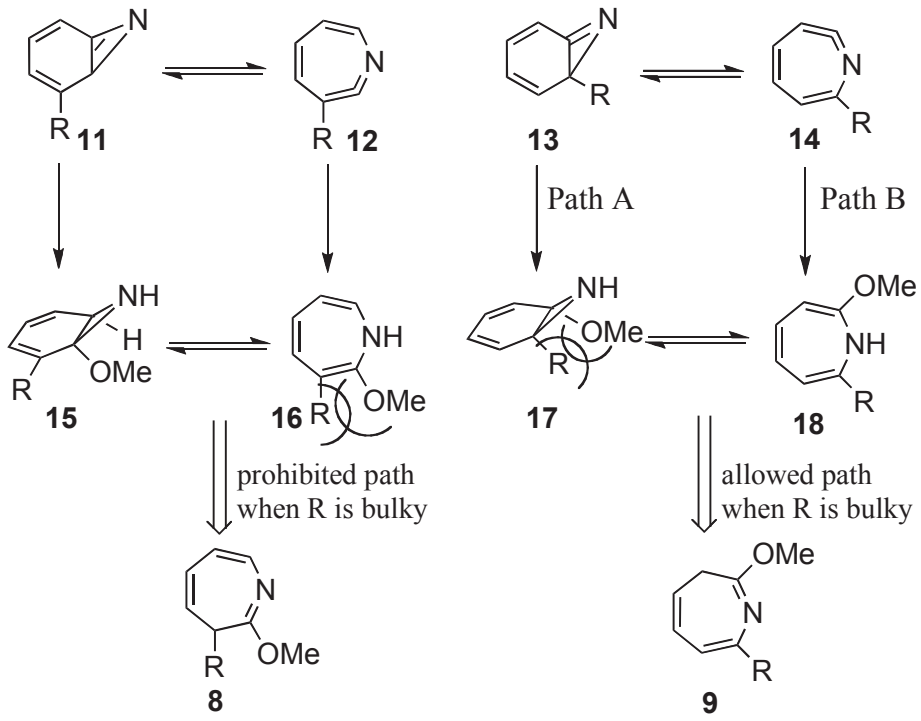
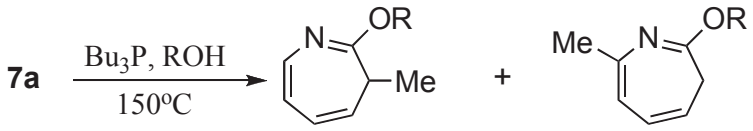


Figure 2. An addition of alcohol to 2,3-dehydroazepine derivatives **12** and/or **14**

In order to confirm the steric effect on the formation ratio between 3-alkyl and 7-alkyl derivatives, nucleophilic media is modified in the reaction of *o*-methylnitrobenzene (**7a**) by methanol, *n*-hexanol, isopropanol and *tert*-butanol (Scheme 2). It has been found that phenylnitrene with small alkyl substituent (such as **7a**) gave 3-methyl and 7-methyl-3*H*-azepine **19a**/**20a** in 1:1 ratio when methanol was used as a NuH. However, reaction of **7a** in the presence of *n*-hexanol gives 3-methyl and 7-methyl-3*H*-azepine **19b**/**20b** in the ratio of 0.33 (Scheme 2).[7] Furthermore, reaction of **7a** using *i*-propanol gives a mixture of **19c** and **20c** in 0.05 ratio and no formation of 3-methyl-3*H*-azepine **19d** were found in the reaction with *tert*-butanol. After all, the observed product distributions support that the regioselective formation of

7-alkyl-3*H*-azepine derivatives depends on the bulkiness of an alcohol used, the formation ratio is fully controlled by the steric features of alcohol adduct on dehydroazepine through path B.



19a-d
19a = 8a

20a-d
20a = 9a

R	Ratio **19**/**20**	Yield **19** + **20** (%)
a: Me	1.00	31
b: *n*-C_6H_{13}	0.33	65
c: ^{i}Pr	0.05	64
d: ^{t}Bu	0.00	54

Scheme 2

Table 1. ^{1}H NMR parameters for the ring protons of 3*H*-azepine derivatives in $CDCl_3$ and GIAO calculated chemical shifts for **8aAx** and **8aEq**

Compound	Chemical Shift (δ, ppm)					$^3J_{H,H}$/Hz			
	H-3	H-4	H-5	H-6	H-7	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$
3-alkyl derivatives									
8a	1.97	5.01	6.16	5.98	6.96	5.5	3.8	5.5	8.3
8aAx	1.58	4.95	6.44	5.91	7.35	-	-	-	-
8aEq	3.16	5.42	6.43	5.74	7.20	-	-	-	-
8b	1.98	5.04	6.18	5.98	6.97	5.5	3.5	5.5	8.0
19b	1.95	4.98	6.16	5.96	6.95	5.5	3.5	5.5	8.0
7-alkyl derivatives									
9a	2.62	5.18	6.13	5.86	-	6.8	4.8	5.5	-
9b	2.34	5.20	6.13	5.84	-	6.5	3.8	5.5	-
9c	2.58	5.20	6.14	5.84	-	6.5	2.8	5.8	-
19c	2.57	5.14	6.12	5.82	-	7.0	2.8	5.5	-
19d	2.49	5.10	6.12	5.78	-	7.0	2.5	5.5	-

The structure of 3*H*-azepine derivatives was characterized by an analysis of chemical shift and $^3J_{H,H}$ coupling constant for ring protons (Table 1). An eminent difference was observed in H-3 chemical shift between 3-alkyl- and 7-alkyl-3*H*-azepines. Usually, the methyne and methylene proton of general di-π-methane moiety are observed at around δ 3.0 and 2.6 ppm, respectively, however, assigned H-3 methyne proton for 3-alkyl-3*H*-azepines (**8a,b** and **19b**) and methylene protons for 7-alkyl-3*H*-azepines (**9a-c** and **20c,d**) are δ 1.95–1.98 and 2.34–2.62 ppm, respectively. This implies that the methyne proton of 3-alkyl azepine is observed by 1 ppm higher field shift compared to usual chemical shift value. To

obtain theoretical information, GIAO chemical shift calculation[9] for the structures **8aAx** and **8aEq**, which are correlated by ring inversion of seven-membered azatriene ring, were performed at HF/6-311+(2d, p)//B3LYP/6-31G(d) levels using GAUSSIAN09[10] software package. Calculated chemical shift for **8aAx** and **8aEq** are included in Table 1 along with experimental data. By comparison between observed H-3 chemical shift for **8a** and calculated values (**8aAx** and **8aEq**), characteristic value of the methyne proton on **8a** is considered to be rather the syn-axial situated proton of **8aAx** than the anti-equatorial proton of **8aEq**. Therefore, chemical shift data explains the equilibrium arises from the ring-inversion lies so far to the left (Figure 3), that is, **8aAx** is a predominant conformer at under ambient conditions. Shielding effect on the proton which situated in the syn-axial position of seven-membered triene system has been explained as an anisotropic effect.[11,12] In addition, optimized energy at B3LYP/6-31G(d) levels of **8aAx** is more stable than **8aEq** by 1.4 kcal/mol in gas phase.

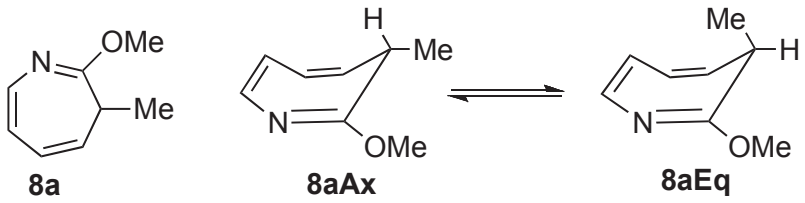


Figure 3. Equlibrium between **8aAx** and **8aEq** by the inversion of 3-methyl-3*H*-azepine ring.

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