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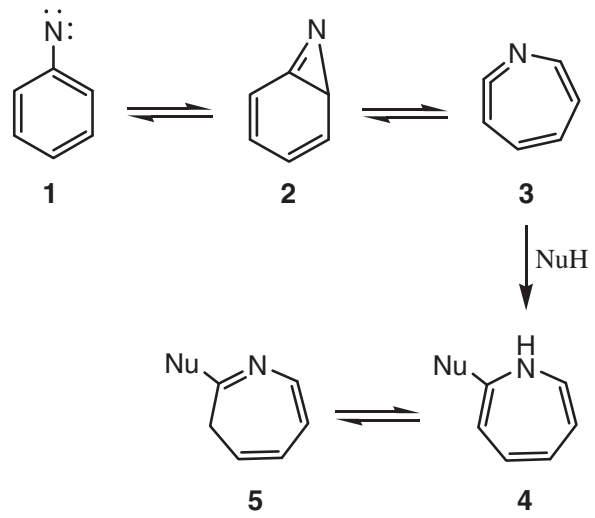
Unprecedented Temperature-dependent Formation of 3- and 7-Methyl-3*H*-azepine Derivatives by the Reaction of *o*-Nitrotoluene with Tributylphosphine in Nucleophilic Media

Siti Mariyah Ulfa, Hideki Okamoto, and Kyosuke Satake*
Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530

(Received December 27, 2011; CL-111233; E-mail: satake@cc.okayama-u.ac.jp)

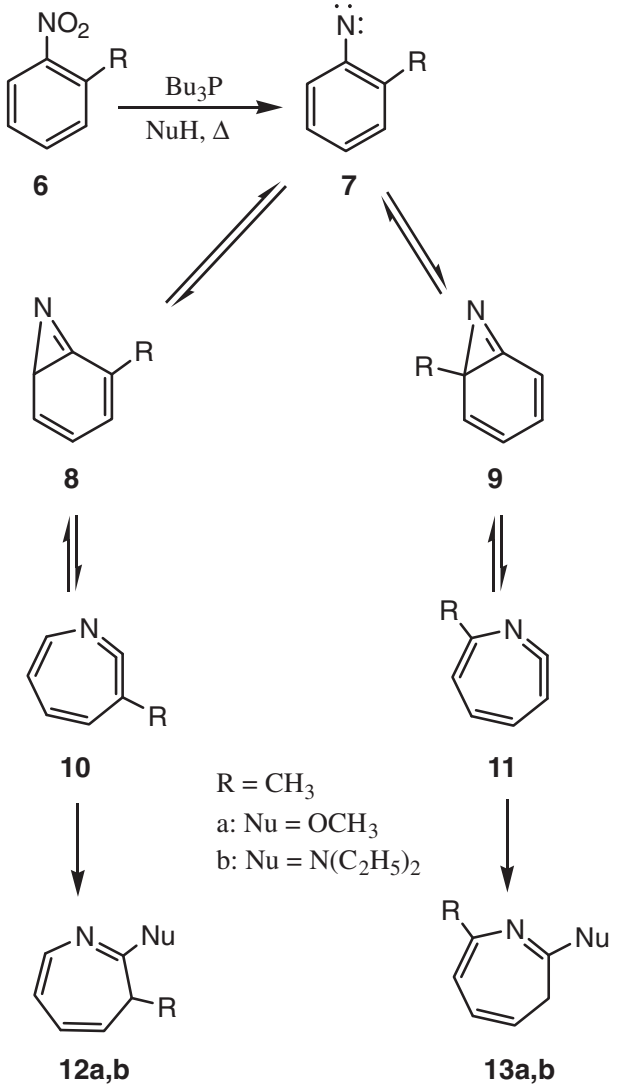
The reaction of *o*-methylphenylnitrene in the presence of alcohol and amine was expected to give isomeric pairs of 3- and 7-methyl-3*H*-azepine derivatives. The formation ratio between these isomers was found to be obviously influenced by reaction temperature, that is, reaction at 150 °C gave 7-methyl-3*H*-azepine derivative, however, it became minor under 70 °C in both media. The ratio between 3- and 7-methyl derivatives is explained by a scheme of kinetic- and thermodynamic-controlled product distribution from *o*-methylphenylnitrene to 3- and 7-methyldehydroazepine intermediates which are trapped by nucleophilic media to give 3- and 7-methyl-3*H*-azepine derivatives.

A number of reports on the synthesis of 3*H*-azepines via phenylnitrene from various starting material have appeared, since Doering and Odum released the synthesis of 2-alkylamino-3*H*-azepines by the photolysis of phenylazide in dialkylamine.[1,2] The reaction has been extended to the thermal degradation of azide in nucleophilic media to obtain 2-substituted 3*H*-azepine derivatives.[3] In addition, deoxygenation of nitro-[4] and nitrosobenzene[5] derivatives by the action of tervalent phosphorus reagent in the presence of alcohol or amine was also established for the synthesis of 3*H*-azepine derivatives.[6] The reaction mechanism giving 3*H*-azepines has been widely discussed based on theoretical calculations[7] and/or sophisticated experimental technique.[1a,8] The formation path for 3*H*-azepine derivative from a generated phenylnitrene[9] **1** is shown in Scheme 1. Intramolecular insertion reaction of **1** leads to a thermodynamically unfavorable benzoazirine intermediate **2**. This step is considered as a rate-determining one throughout this reaction pathways.[10] The following concerted ring expansion gives dehydroazepine intermediate **3**. The process including nitrene **1**, benzoazirine **2**, and dehydroazepine **3** has been thought to be reversible.[11] Finally, addition of nucleophilic media such as alcohols or dialkylamines on the C=N bond of **3** gives 2-substituted 3*H*-azepines **5** via labile 1*H*-azepine **4**. According to this scheme, when *o*-alkylnitrobenzene **6** is employed as a starting material, the formation of benzoazirines **8** and **9** can be expected by an insertion reaction at or away from the *o*-substituent of nitrene **7** (Scheme 2). Each isomerizes by a concerted ring-opening to give 3-alkyl- and 7-alkyldehydroazepine **10** and **11** which are trapped by nucleophilic media and subsequently give an isomeric pair of 2-substituted 3*H*-azepines **12** and **13**. The simultaneous formation of both isomers has not been known until our recent research on the synthesis of alkyl-substituted 3*H*-azepine derivatives from *o*-alkylphenylnitrene. We reported the first isolation of respective isomer along with the substituent effect on the formation ratio between isomers 3- and 7-alkyl-substituted 3*H*-azepines **12** and **13** from the reaction of *o*-alkylnitrobenzene (alkyl = *t*-Bu, *i*-Pr, Et, and Me) and tributylphosphine (Bu_3P) in an alcoholic media by heating at 150 °C in a sealed tube.[12] Nitrobenzene with a smaller *o*-substituent such as *o*-nitrotoluene gave **12** and **13** by 1:1 ratio, however, *o*-*t*-butylnitrobenzene gave **13**, exclusively in methanol under similar conditions.[13] Here, we report the temperature-dependent effect on the formation ratio between **12** and **13** in the reaction of *o*-nitrotoluene (**6**, R = Me in Scheme 2) and Bu_3P in the presence of methanol and diethylamine (DEA) at 150 °C and at decreased temperature.



Scheme 1.

A solution of **6** (5 g, 36.5 mmol) and 2 equiv of Bu_3P in methanol (25 mL) was degassed by nitrogen flow for 1 h, then heated in a stainless sealed tube at 100 °C for 24 h. Excess methanol was removed and the resulting mixture was distilled under reduced pressure. The fraction from 55 to 60 °C at 29 Torr was a mixture of 2-methoxy-3- and 2-methoxy-7-methyl-3*H*-azepines (**12a** and **13a**, 1.25 g, 25%) as a colorless oil. The ratio between **12a** and **13a** (**12a**:**13a** = 90:10) was determined by ^{1}H NMR integration value of $\delta_{H\text{-}4}$ 5.01 (dd, J = 5.5 and 8.5 Hz) for **12a** and $\delta_{H\text{-}4}$ 5.18 (td, J = 6.8 and 8.5 Hz) for **13a**, respectively. Chromatographic separation of the mixture using a silica gel column with a cooling jacket at 0 °C (AcOEt:hexane (1:19 v/v)) gave pure **12a** and **13a** without decomposition.[14] On heating the starting mixture in a sealed tube at 70 °C for a week, **12a** and **13a** were obtained in 16% yield[15] with the formation ratio of **12a**:**13a** = 99:1. Although the reaction at 150 °C did not show any selectivity in the formation of an isomeric pair, an obvious selectivity was observed on the formation of **12a** and **13a** under at decreased temperature (Table 1).



Scheme 2.

Reaction using DEA as a nucleophilic media was also carried out to investigate the temperature dependency in the formation ratio between **12b** and **13b**. A degassed solution of **6** (5 g, 36.5 mmol), 2 equiv of Bu_3P and DEA (34 mL) was heated in a stainless sealed tube at 150 °C for 24 h. After cooling, the excess of DEA was removed and the residue was distilled under reduced pressure to give the mixture of 2-diethylamino-3- and 2-diethylamino-7-methyl-3*H*-azepine (**12b** and **13b**) in 49% yield as a pale yellow oil. The ratio between **12b** and **13b** was determined (**12b**:**13b** = 20:80) by the integral value of $\delta_{H\text{-}4}$ 5.16 (pseudo t, $J = 9.2$ Hz) for **12b** and $\delta_{H\text{-}4}$ 5.00 (td, $J = 7.2$ and 8.4 Hz) for **13b** in the ^{1}H NMR spectrum of the mixture. To isolate the isomers from a distilled mixture, reverse-phase chromatography was carried out using acetonitrile (MeCN) as an eluent. Each of the structures were characterized by the ^{1}H NMR resonance peak from the above described H-4 proton and methyl group attached on the seven-membered ring. Methyl peaks of compound **12b** and **13b** were observed at δ 0.70 (d, $J = 7.0$ Hz) and 2.09 (s), respectively.[16] Reactions at 100 and 70 °C for 24 h in a stainless sealed tube also gave a mixture of **12b** and **13b** in

Table 1. Yields and formation ratios between 3*H*-azepines **12** and **13**

Reaction temp/°C	Time/h	Solvent	Ratio/% **12**:**13**	Yield/% **12** + **13**
150	24	MeOH	50:50	31[a]
100	24		90:10	25
70	7 days		99:1	16
150	24	$HNEt_2$	20:80	49
100	24		67:33	24
70	24		91:9	21

[a]Reference 12.

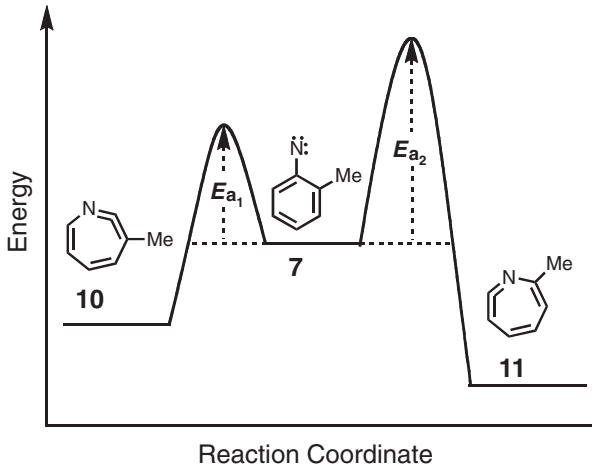


Figure 1.

24 and 21% yield and in the ratio of **12b**:**13b** = 67:33 and 91:9, respectively. Reaction at 150 °C gave 7-methyl derivative **13b** as a main product over 3-methyl derivative **12b**, however, the ratio between **12b** and **13b** altered under at 100 °C. When the reaction was carried out at 70 °C, **12b** was selectively obtained as a major product (Table 1).

In order to examine the behavior of final products, isolated **12a** and **12b** were heated at 150 °C for 24 h in a glass sealed tube in methanol/Bu_3P and DEA/Bu_3P, respectively. Isomerizations from **12** to **13** were not observed in the reaction mixture in both cases. This means that the final nucleophilic addition step is irreversible, therefore the formation ratio between **12a**, **12b** and **13a**, **13b** reflects the ratio between intermediary dehydroazepines **10** and **11**. Such temperature-dependent results are frequently explained by kinetic- and thermodynamic-controlled product distribution with requirement of whole steps should be reversible. Insertion reactions giving intermediates **8** and **9** are parallel reactions, however, Tsao et al.[10b] reported the reaction toward **8** is faster than the other. In addition, according to a theoretical study on insertion of *o*-substituted phenylnitrene was reported by Sunberg et al.[1b,17] the predicted transition structure from **7** to **8** was more stable than from **7** to **9** and the insertion reaction was the rate-determining step. Accordingly, an apparent activation energy E_{a_1} giving **10** believed to be small compared to E_{a_2} giving **11** (Figure 1).[18] To obtain the theoretical information on relative thermodynamic stability of dehydroazepines **10** and **11**, B3LYP/6-31G* levels calculation was carried out

using Gaussian09 software package.[19] Calculation predicted that an optimized intermediate **11** ($E = -325.6080036$ hartree) was slightly more stable than **10** ($E = -325.6041176$ hartree) by 2.44 kcal mol^{-1}. Based on this information, the energy profile from *o*-methylphenylnitrene **7** to 3- and 7-methyldehydroazepine intermediates **10** and **11** can be represented as in Figure 1. At lower temperatures, the reaction is controlled kinetically to give **12a** and **12b** as a main product via dehydroazepine **10**. On the other hand, **13a** and **13b** becomes the major product at elevated temperature via thermodynamically stable intermediate **11** even though the reaction rate giving precursor **9** is thought to be slow because of higher activation energy E_{a_2}.

Here presented results show the influence of reaction temperature on the formation ratio between 3- and 7-methyl-3*H*-azepine derivatives when *o*-methylphenylnitrene is generated by the deoxygenation of *o*-nitrotoluene using Bu_3P in nucleophilic media such as alcohol and amine. Observed temperature-dependent product distribution can be explained by kinetic- or thermodynamic-controlled product distribution. Detailed mechanistic study on this reaction is under investigation.

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16 ^{1}H NMR spectrum data of **12b** (400 MHz, $CDCl_3$): δ 0.70 (d, $J = 6.8$ Hz, 3H), 1.13 (t, $J = 6.8$ Hz, 6H), 3.36 (m, 4H), 4.15 (br, 1H), 5.16 (pseudo t, $J = 9.2$ Hz, 1H), 5.61 (dd, $J = 6.0$ and 8.0 Hz, 1H), 6.26 (dd, $J = 6.0$ and 9.2 Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 18.5, 43.7, 44.1, 108.4, 117.0, 128.0, 139.5, 148.2; IR ν_{max}(film): 2970, 1554, 1511, 1356, 1253, 720, 681 cm^1; UV–vis (EtOH): λ_{max} 303 nm ($\log \varepsilon = 3.83$). **13b** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, $J = 6.8$ Hz, 6H), 2.09 (s, 3H), 2.62 (br, 2H), 3.36 (q, $J = 6.8$ Hz, 4H), 5.00 (dt, $J = 7.2$ and 8.4 Hz, 1H), 5.65 (d, $J = 5.6$ Hz, 1H), 6.21 (dd, $J = 5.6$ and 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 26.5, 31.6, 43.0, 107.1, 109.6, 128.9, 142.9, 149.8; IR ν_{max}(film): 2971, 1561, 1525, 1350, 1343, 710, 639 cm^1; UV–vis (EtOH): λ_{max} 294 nm ($\log \varepsilon = 3.78$).

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18 We also confirmed E_{a_1} is smaller than E_{a_2} by 3.43 kcal mol^{-1} based on respective energy for transition state structure (−325.5913417 and −325.5858779 hartree) at B3LYP/6-31G* levels calculation.

19 Software employed: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09 (Revision A.1)*, Gaussian, Inc., Wallingford CT, **2009**.

