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Shortcut Approach to 1,4-Diazepine from 3-Pyridylnitrene Intermedietes under Mild Condition

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ABSTRACT

The reaction of nitropyridine derivatives and tributylphosphine (Bu_3P) with the existence of nucleophilic solvent gives ring expansion product as diazepines in medium yield. Reaction mechanism subjected the formation of phenylnitrene, followed by intramolecular electrophilic insertion reaction to pyridine ring and subsequent ring enlargement. The intermediate in the reaction confirmed by computational calculation using B3LYP/6-31G* level. The intramolecular insertion reaction of pyridylnitrene is considered suppressed by the low HOMO (-9.932 eV) energy level of pyridine ring compared to that of benzene (-9.653 eV), hence 1,4-diazepine is obtained when employed 3-nitro-2,6-lutidine as starting material. The formation of diazepines was confirmed by the analysis of ^{1}H NMR data. Separation of the product mixture using column chromatography on SiO_2 was carried out and found to give expected diazepine along with the reduction product.

Key word: nitropyridine, diazepine, ring expansion, regioselective, pyridylnitrene

INTRODUCTION

Although photochemical rearrangements are powerful ways to synthesize heterocyclic compounds, their use is often hindered by the technical difficulties when the materials are in large quantities [1,2]. The more convenient system is thermal reaction, which handled sample over ten times larger and give a selective product. Thermolysis of azido-, nitro-, and nitrosobenzenes have been reported by many workers to undergo ring expansion *via* azirine intermediate in the presence of bases [3,4]. However, the reaction of monocyclic pyridylazides or nitropyridines were hitherto unexplored.

The 1,2-diazepines, 1,3-diazepines, and 2,3-benzodiazepines have been synthesized, as well as related fused diazepines condensed with aromatic heterocyclic rings. Among the three possible monocyclic diazepines, the 1,2-diazepines have been most widely studied because its pharmaceutical application. Of the 1,3- and 1,4-diazepines, only 1-acyl-1*H*-1,3-diazepines and the highly substituted 6*H*-1,4-diazepines had been reported [5,6].

The photolysis of 4-azidopyridines in the presence of sodium methoxide resulted the formation of 6*H*-1,4-diazepine *via* azirine intermediates and subsequent acylation gave 1-acyl-1*H*-1,4-diazepines [7]. Photochemical behavior of 3-azidopyridines under basic condition has been reported to give 1,3-diazepines, whereas the photolysis of 2-substituted 3-azidopyridines having no substituent at 4-position gave the novel 2*H*-1,4-diazepines

framework [8]. The excellent result from photolysis azidopyridines to diazepines prompted us to examine the behavior of non-toxic starting materials, nitropyridines derivatives, reacted with Bu_3P in the presence of nucleophile. Electron attracting N-substituents in the ring expected to support the abstraction of oxygen in deoxygenation process leads to pyridylnitrene and dehydroazepine intermediate [9].

EXPERIMENT

Chemicals and instrumentation

All chemicals used for this research were purchased from Wako Pure Chemical Industries or other specified.

The ^1H and ^{13}C NMR spectra were recorded on a Varian 500 and/or INOVA 600 NMR system. Infrared spectra were recorded on an IRPRESTIGE-21 SHIMADZU Corporation. Fast Atom Bombardment (FAB) and High Resolution Mass Spectra (HRMS) were obtained from JEOL mass spectrometer. Elemental analysis was performed on a PERKIN ELMER 2400II. Melting point was measured on a Yanagimoto micro melting point apparatus. UV-visible absorption was recorded on a JASCO V-530 spectrophotometer. Thin-layer chromatography (TLC) was performed on Silica-gel 60 F_{254} (Merck). The molecular orbital calculations were carried out on personal computer UNITCOM Intel Core 2 Quad computer system.

Procedure reaction

Synthesis of 3-nitropyridines (2)

Preparation of **2** based on Katrizky methods as follows [10]. Trifluoroacetic anhydride (10 ml, 42 mmol) was chilled in an ice bath and, 17 mmol of pyridines (**1**) were slowly added and stirred at chilled conditions for 2 h followed by the dropwise addition of concentrated nitric acid (1.9 ml, 36 mmol). After stirring for 18 h, the solution was dripped slowly into a chilled aqueous solution of sodium metabisulfite (3.2 g, 17 mmol in 25 ml water). After 24 h, the solution was brought to pH 6–7 from pH 2–3 by addition of 25% NaOH solution, extracted with methylene chloride and the extract was dried over anhydrous sodium sulfate. The solvent was evaporated and further purified by column chromatography using hexane/ethyl acetate (3:7) gave **2** (Y = 41%): yellow pale crystal, mp 38.5–39.5 ^oC; IR ν_{max} (KBr) 1520, 1352 (N=O) 1195, 1017 (C-N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.3, and 0.5 Hz, 1H), 8.02 (ddd, *J* = 8, 2.7, 2.7 Hz, 1H), 8.93 (dd, *J* = 4.5, 1.5 Hz, 1H), 9.47 (d, *J* = 2.5 Hz, 1H).

Synthesis of 3-nitro-2,6-lutidine (4)

The following procedure was dictated from Plazek [11]. 2,6-Dimethylpyridin (15 g) (**3**) was gradually dissolved in 70 ml fuming (smoking) sulfuric acid containing 28% of SO_3. After 30 minute, 25 g KNO_3 gradually added and heating in water bath for 5 hours. After cooling down, **4** will separate as crystal over the water surface. Now, extract 2 times using 400 ml of ether then dried over using KOH, evaporated ether and distill the residue. The ether-residue was distilled out as first fraction until 160 ^oC (4.5 g); then the temperature rose rapidly, and the largest part of the reaction product will pass over between 220–230 ^oC. The distillate solidified in the receiver. A repeated distillation delivered the pure nitro compound of the bp 227 ^oC and mp 37 ^oC (14 g, Y = 83%). Nitrolutidin **4** is a clear pale crystal, insoluble in water and easily dissolved in organic solvent; IR ν_{max} (KBr): 2920, 2860 (CH_3)

1518, 1352 (N=O) 1265 (N=O, aromatic) 1158, 1031 (C-N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.62 (s, 3H), 2.84 (s, 3H), 7.17 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H).

Synthesis of 3-Aminopyridine (5)

A mixture of **2** (75 mmol), Bu_3P (172 mmol), and methanol (624 mmol) was heated in a sealed tube at 110 ^oC for 24 hours. The obtained reaction mixture was evaporated using rotary evaporator to distil the excess of solvent. The product mixture was purified by open column chromatography using ethyl acetate/hexane. Aminopyridine **5** [12] was identified as brown solid, mp 63 ^oC (hygroscopic), blue fluorescent spot on TLC plate; ^1H-NMR (500 MHz, $CDCl_3$): 3.65 (br), 6.98 (m, 1H), 7.07 (dd, *J* = 4.75, 8.5 Hz, 1H), 8.02 (d, *J* = 3.5 Hz, 1H), 8.09 (d, *J* = 2.5 Hz, 1H).

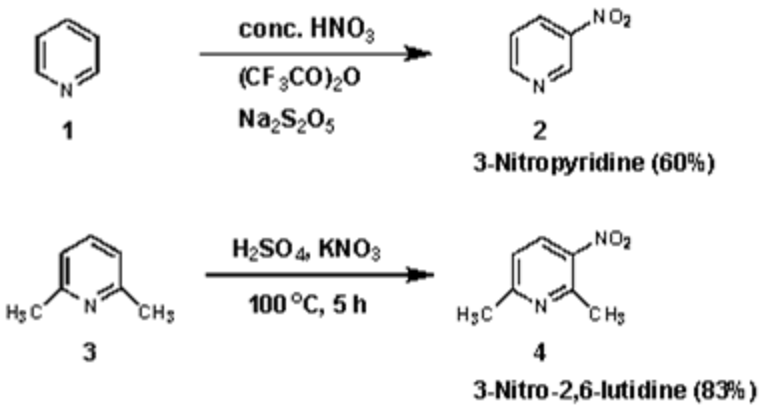
Synthesis of 3-Methoxy-2,7-dimethyl-2H-1,4-diazepines (6)

A mixture of **4** (75 mmol), Bu_3P (172 mmol), and methanol (624 mmol) was heated in a sealed tube at 110 ^oC for 24 hours, then the excess of solvent was evaporated using rotary evaporator under reduced pressure. The product mixture was separated by silica gel column chromatography using ethyl acetate. The physical properties of **6** were reddish-yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.67 (3H, d, *J* = 6.75 Hz), 2.14 (3H, s,), 3.11 (1H, q, *J* = 6.65 Hz, C2-H), 3.74 (3H, s), 6.12 (1H, d, *J* = 8 Hz, C6-H), 7.04 (1H, d, *J* = 8 Hz, C5-H). The NMR data was comparable with Sawanishi reported result [8].

RESULT AND DISCUSSION

Synthesis of nitropyridine derivatives

In the effort to synthesize 1,4-diazepines, nitropyridines were selected as starting material. 3-Nitropyridine (**2**) and 2,6-dimethyl-3-nitropyridine (a compound with the common name 3-nitro-2,6-lutidine, **4**) was prepared by direct nitration of pyridine derivatives (Scheme 1). The starting 3-nitropyridine (**2**) was synthesized according to the procedures reported by Katritzky and co workers (see Experimental section). Treatment of pyridines (**1**) with nitric acid in trifluoroacetic anhydride (TFAA) and subsequent addition of sodium metabisufite followed by extraction with dichloromethane afforded **2** (41%), as pale yellow crystal, mp 38.5–39.5 ^oC. The characterization product was confirmed by comparing the physical properties and chemical shift of ^1H NMR spectrum with published data [10].

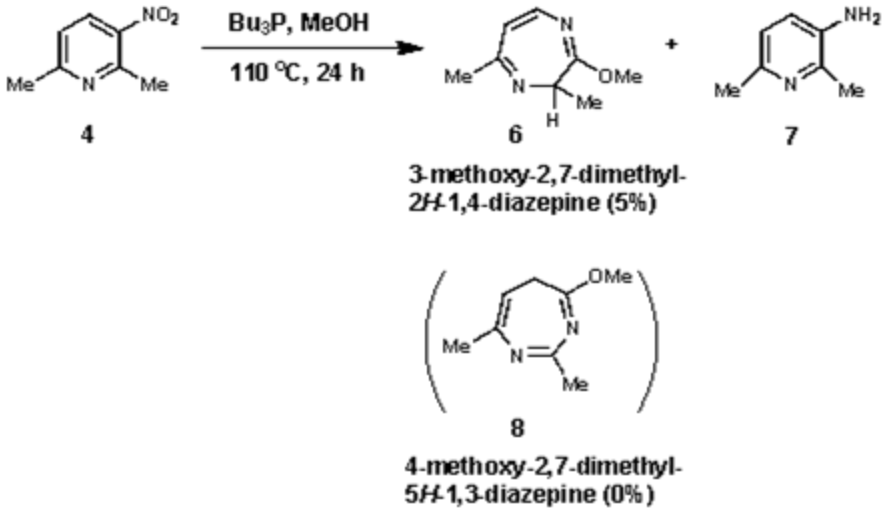


Scheme 1. Synthesis of nitropyridine derivative

Nitration of 2,6-lutidine (**3**) to give 3-nitro-2,6-lutidine (**4**) was proposed by Plazek procedure [11]. Dissolved 2,6-lutidine in fuming sulfuric acid, and added with potassium nitrate followed by extraction in ether afforded 3-nitro-2,6-lutidine (**4**) as separated crystal over water surface (Y = 83%). The physical properties and ^{1}H NMR spectrum of **4** is in agreement with the reported data.

Reaction of nitropyridine derivatives with Bu_3P

A general procedure for the reaction of **2** and **4** is as follows. A mixture of **2** in the presence of methanol was added with 2 equiv. of Bu_3P and flowed by nitrogen gas for an hour to prevent the oxidation of Bu_3P to phosphine oxide, then heated in sealed tube at 110 ^oC for 24 h. The obtained reaction mixture was separated using column chromatography. The product obtained from this reaction was elucidated as 3-aminopyridine (**5**). The obvious chemical shift of amino substituent was observed (–NH_2) as broadening peak at 3.65 ppm which exchangeable with D_2O solvent. The structure of **5** was also confirmed by identical ^{1}H NMR spectra to those previously reported [12]. The determined products were subjected as reduction product from the nitro group attached on pyridine ring. This product often reported as by-product by the formation of singlet nitrene in the intermediate step of reaction. It is reported that the deoxygenation of nitro-derivatives compound is temperature-dependent-reaction [13]. The theoretical calculation support an experimental results, since intramolecular insertion reaction of pyridylnitrene is considered to be suppressed by the lower HOMO (-9.932 eV) energy level of pyridine ring compared to that of benzene (-9.653 eV), then ring expansion product should be difficult to be obtained.



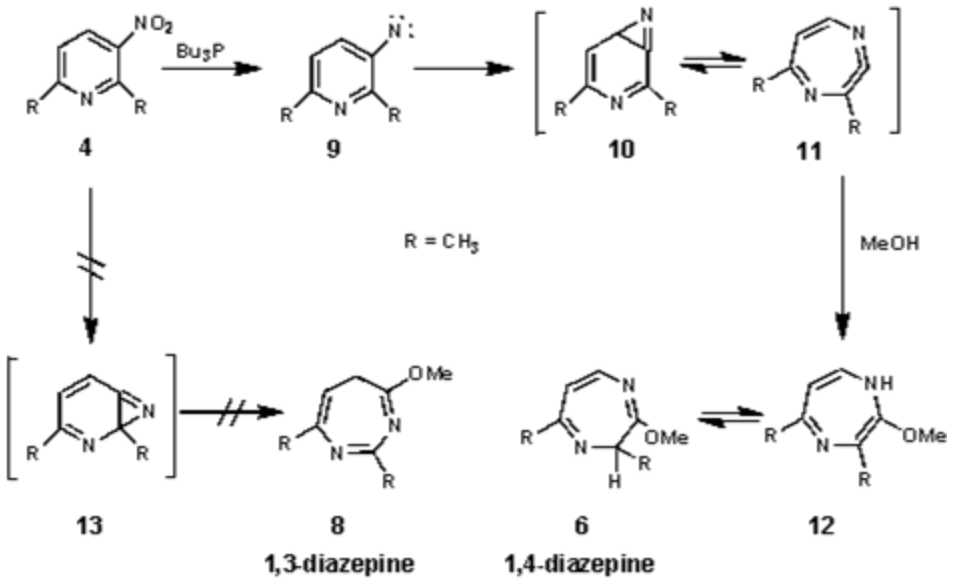
Scheme 2. Reaction of 3-nitropyridine with Bu_3P in the presence of methanol

Similar reaction condition was applied to 2,6-lutidine (**4**) with Bu_3P (2 equiv.) in the presence of methanol, heated in the sealed tube at 110 ^oC for 24 h (Scheme 2). After separation by silica gel column chromatography, 3-methoxy-2,7-dimethyl-2*H*-1,4-diazepine (**6**) was obtained, as well as reduction products **7** and dimerization product **8**. The structure of the 1,4-diazepine **6** was elucidated mainly from their ^{1}H NMR spectral data. An AB pair of doublets (J = 8 Hz) at δ 6.12 and 7.04 is assignable for olefinic of C6-H and C5-H,

respectively, and the former coupled for the methyne proton at δ 1.67 (3H, d, *J* = 6.75, C2-Me) and 3.11 (1H, q, *J* = 6.65, C2-H) also observed. The ^{1}H NMR spectrum and physical properties of **6** were confirmed by reported data [10].

Plausible mechanism reaction

In general, mechanism formation of diazepines was similar with azepines, initiated by the generation of azirine intermediate, formed from the initially generated 3-pyridylnitrenes which cyclized, either to 4-position gives 1,4-diazepine **6** or 2-position to 1,3-diazepine **8** derivatives. Then, addition of methanol to the C=N cumulene system followed by 1,3-prototropic gave **6** or **8** derivatives (Scheme 3). However, the cyclization at 2-position lead to **8** was not observed. Diazepine **6** is relatively unstable and gradually decomposed upon standing, this may account for the decrease in the isolated yields.



Scheme 3. Plausible mechanism reaction formation of 1,4-diazepine

The above result is analogous to that reported by Tsuchiya *et al.* concerning the cyclization orientation of 3-pyridylnitrene. The cyclization of 3-pyridylnitrene, generated from deoxygenation of 3-nitro-2,6-lutidine (**4**), having two methyl group, will predominantly occurred at 4-position to give 1,4-diazepines *via* the azirine. This behavior is similar with 2-substituted phenylnitrenes, which are known to cyclize preferentially at the vacant α-position [7]. In contrast, initial intramolecular cyclization of compound without substituent at 2-position, will predominantly cyclize at the 2-position of the pyridine ring rather than at 4-position to form the azirine **10** and **13**, respectively. For the phenylnitrene which has a substituent at 3-position **14** (Figure 1), in which electron withdrawing groups favor cyclization at the 2 position [7]. Furthermore, the electron withdrawing effect of the ring nitrogen would favor cyclization at the 2-position of the pyridine ring, as shown in the structure **15**, even in the case **16** having an electron withdrawing group at the 5-position, the nitrene gave the 1,3-diazepine skeleton **9**.

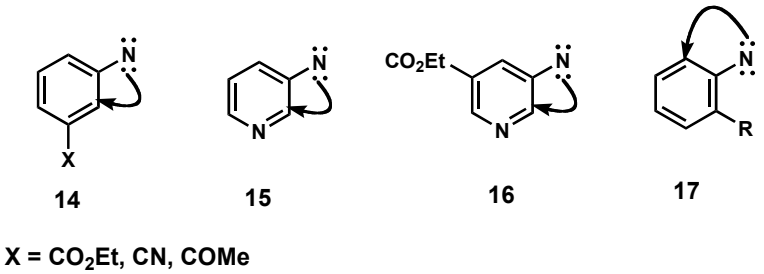


Figure 1. Cyclization direction of alkylnitrene

Energy calculation of intermediates

The theoretical calculation over the intermediate and the products often conducted to give a better insight into the whole mechanism. The calculation of intermediate species involved in the reaction 3-nitro-2,6-lutidine (**4**) to 2*H*-1,4-diazepine (**6**) was carried out using B3LYP/6-31G* level of theory [14]. The result showed that cyclization at 4-position leads to the more stable azirine **10**, but rearrangement to dehydroazepine form is energetically unstable (Figure 2). Since 1,4-diazepine **6** was experimentally observed as a sole product, we proposed that its formation was kinetically favorable product. However, the formation of 1,3-diazepine **9** derivatives may consider as thermodynamically control reaction. Further experimental data is needed to observe the temperature control reaction.

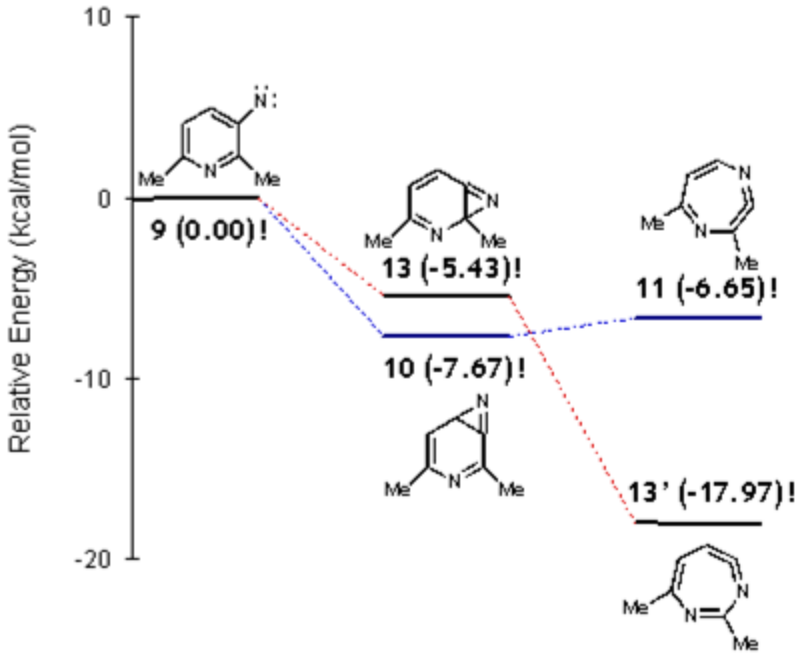


Figure 2. Energy calculation of azirine and dehydroazepine intermedietes

CONCLUSIONS

Reaction of 3-nitropyridine (**2**) and Bu_3P gives 3-aminopyridine (**5**) and 3-nitro-2,6-lutidine (**4**) affords 3-methoxy-2,7-dimethyl-2*H*-1,4-diazepine (**6**). The different products among these reactions were considered by the lower HOMO energy level of pyridine (-9.932

eV) compared to 2,6-lutidine (-9.403 eV). The cyclization of 3-pyridylnitrene has 2-substituted alkyl group is predominantly occurred at 4-position to give 1,4-diazepine. Selective formation of 1,4-diazepine **6** is considered by kinetically stable of dehydroazepine intermediate as precursor of **6**.

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