Synthesis of Dihydropyrroles by the Intramolecular Addition of Alkylideneaminyl Radicals Generated from *O*-2,4-Dinitrophenyloximes of γ,δ-Unsaturated Ketones

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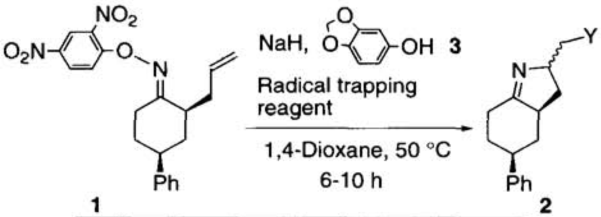
Alkylideneaminyl radicals are generated from *O*-2,4-dinitrophenyloximes of γ,δ-unsaturated ketones by treatment with NaH and 3,4-methylenedioxyphenol. The resulting radical species successively add to the olefinic moiety intramolecularly to afford 3,4-dihydro-2*H*-pyrroles.

Alkylideneaminyl radicals have been utilized as reactive intermediates for the synthesis of nitrogen-containing heterocycles.[1,2] For example, 2,3,4-triphenylquinoline was prepared *via* alkylideneaminyl radicals generated by treatment of (1,2,3,3-tetraphenylpropylideneaminooxy)acetic acid with $K_2S_2O_8$,[2a] and the radical cyclization was taken place by treating each of sulphenylimine,[2b] *O*-phenylselenomethyloxime,[2c] *O*-benzoyloxime,[2d] or 1*H*-benzotriazol-1-ylimine[2e] of 2-allylcyclohexanone with tributylstannane to give 3,3a,4,5,6,7-hexahydro-2-methyl-2*H*-indole.

Recently, we have reported that the cyclization of 2-(3-hydroxyphenyl)ethyl ketone *O*-2,4-dinitrophenyloximes proceeds on the oxime nitrogen atom by treatment with NaH in 1,4-dioxane to afford quinolin-8-ols and their 1,2,3,4-tetrahydro derivatives.[3] This cyclization is initiated by single electron transfer from the phenolate moiety to the 2,4-dinitrophenyl group, and the successive N-O bond cleavage results in the formation of alkylideneaminyl radicals, which are then coupled to afford quinoline derivatives.[3c] Herein, we would like to report a synthetic method of 3,4-dihydro-2*H*-pyrroles by the radical cyclization generated from *O*-2,4-dinitrophenyloximes of γ,δ-unsaturated ketones by single electron transfer reaction.

First, *cis*-4-phenyl-2-(2-propenyl)cyclohexanone (*E*)-*O*-2,4-dinitrophenyloxime (**1**) was chosen as a model compound, and was treated with NaH in 1,4-dioxane in the presence of various phenol derivatives as electron donating agents and 1,4-cyclohexadiene as a radical trapping reagent. Among several phenols examined, such as *m*-cresol, *p*-hydroquinone, *p*-methoxyphenol, 3,4-methylenedioxyphenol, and *p*-*N*,*N*-dimethylaminophenol, 3,4-methylenedioxyphenol (**3**) was found to be a suitable one. When a mixture of the oxime **1**, NaH, **3**, and 1,4-cyclohexadiene in 1,4-dioxane was heated to 50 °C, a cyclized product, 3,3a,4,5,6,7-hexahydro-2-methyl-5-phenyl-2*H*-indole (**2a**), was obtained in 91% yield (Table 1, Entry 1).[4] Some other radical trapping reagents, such as carbon tetrachloride, diphenyl disulfide, and diphenyl diselenide, were also utilized as the radical terminators instead of 1,4-cyclohexadiene, and chloromethyl **2b**, phenylthiomethyl **2c**, and phenylselenomethyl hexahydroindoles **2d** were produced in 75%, 70%, and 69% yields, respectively (Table 1, Entries 2-4).

Table 1. Cyclization of *O*-2,4-dinitrophenyloxime **1**[a]



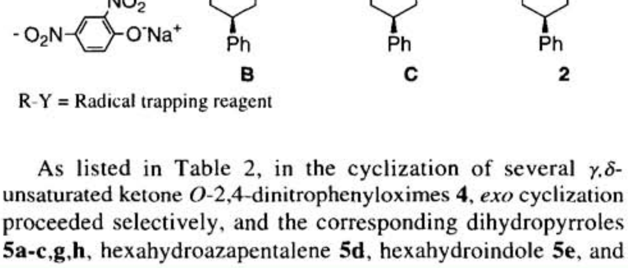
1 **2**

Entry	Radical trapping reagent	Product **2**[d] Y	Yield / %	
1	 [b]	H	91	**2a**
2	CCl_4[b]	Cl	75[e]	**2b**
3	PhSSPh[c]	SPh	70[e]	**2c**
4	PhSeSePh[c]	SePh	69[e]	**2d**

[a] 10 equimolar amounts of NaH and an equimolar amount of **3** were used.
[b] 10 equimolar amounts of reagent was used.
[c] 3 equimolar amounts of reagent was used.
[d] Diastereomer ratio=2:1.
[e] **2a** was given as a by-product in about 10% yield.

This cyclization proceeds as shown in Scheme 1. Firstly, treating of the oxime **1** with NaH and 3,4-methylenedioxyphenol **3** induces electron transfer from sodium phenolate to the dinitrophenyl group to generate an anion radical **A**. The N-O bond of the oxime moiety cleaves to provide an alkylideneaminyl radical **B** and sodium 2,4-dinitrophenolate. The intramolecular trapping of **B** by the olefinic moiety and the successive termination of a cyclized radical **C** give the dihydropyrrole **2**.

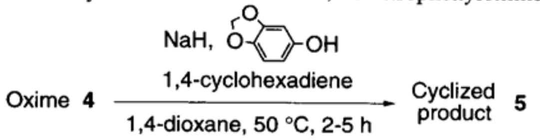
Scheme 1. The mechanism of the cyclization of oxime **1**.

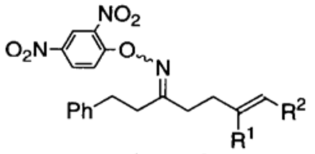
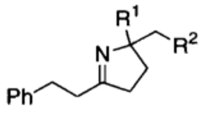
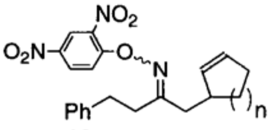
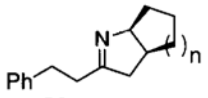
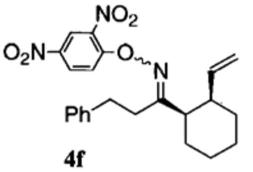
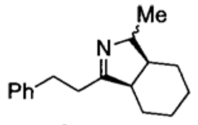
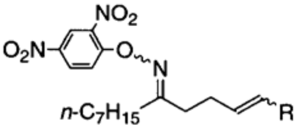
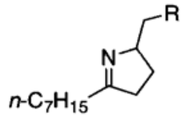


R-Y = Radical trapping reagent

As listed in Table 2, in the cyclization of several γ,δ-unsaturated ketone *O*-2,4-dinitrophenyloximes **4**, *exo* cyclization proceeded selectively, and the corresponding dihydropyrroles **5a-c,g,h**, hexahydroazapentalene **5d**, hexahydroindole **5e**, and hexahydroisoindole **5f** were prepared in good yield. As the reaction of either *E*- or *Z*-isomer of the oximes **4a** gave **5a** in the same yield, the reaction could be performed by using a mixture of the *E*- and *Z*-isomers.[3c]

Table 2. Cyclization of several *O*-2,4-dinitrophenyloximes **4**

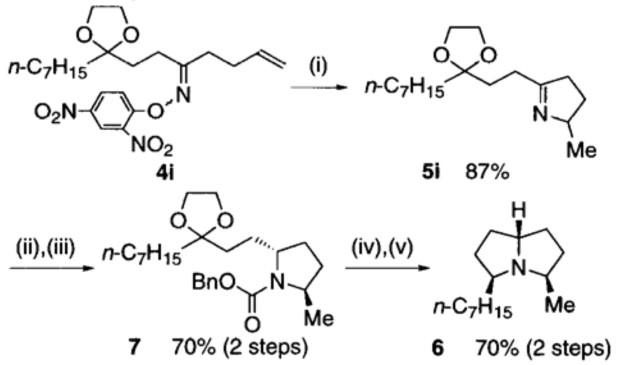


Oxime **4**	Cyclized product **5**
	
4a (R^1=H, R^2=H)	**5a** 80%
4b (R^1=Me, R^2=H)	**5b** 72%
4c (R^1=H, R^2=Ph)	**5c** 70%
	
4d (n=1)	**5d** 86%
4e (n=2)	**5e** 85%
	
4f	**5f**[a] 72%
	
4g (R=Me)	**5g** 54%
4h (R=$CH_2CH(OSi$*t*$\text{-}BuMe_2)Me$)	**5h** 72%

[a] Diastereomer ratio=3:1.

This method was applied to the synthesis of xenovenine (**6**), a bicyclic 3,5-dialkylpyrrolizidine alkaloid isolated from the cryptic thief ant *Solenopsis xenovenium*.[5] An oxime **4i**, prepared from oxalyl chloride in 6 steps, was treated with NaH, **3**, and 1,4-cyclohexadiene in 1,4-dioxane at 50 °C to afford a dihydropyrrole **5i** in 87% yield. It has been known that the hydrogenation[6c] or the metal hydride-reduction (e.g. DIBAH)[6a] of 2,5-disubstituted 3,4-dihydro-2*H*-pyrroles gives 2,5-*cis*-disubstituted pyrrolidines selectively. In contrast, stereoselective reduction of dihydropyrroles to 2,5-*trans* pyrrolidine has remained to be established: The $NaBH_4$ reduction in acetic acid afforded the 2,5-*trans* isomer preferentially, but in only 70:30 ratio.[6a,b] It was found that the dihydropyrrole **5i** was converted to an enecarbamate by treatment with benzyl chlorocarbonate, and successively reduced with $NaBH_4$ in acetic acid to obtain the 2,5-*trans*-disubstituted pyrrolidine **7** exclusively in 70% yield. Deacetalization of **7** and the successive hydrogenation provided the desired pyrrolizidine **6** as a single diastereomer in 70% yield.

Scheme 2. Synthesis of xenovenine **6**[a].



a Reagents: (i) NaH, 3, 1,4-cyclohexadiene, 1,4-dioxane, 50 °C, 2 h ; (ii) BnOCOCl, Et3N, toluene, rt; (iii) NaBH4, AcOH, rt; (iv) 1M HClaq., THF, rt; (v) H2 (1 atm), Pd/C, MeOH, rt.

As mentioned above, a new method for the generation of alkylideneaminyl radicals has been developed by single electron transfer process. The radical species generated from γ,δ-unsaturated ketone *O*-2,4-dinitrophenyloximes are captured with the olefin moiety intramolecularly, giving a variety of dihydropyrrole derivatives.

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References and Notes

1 For an excellent review of the generation of alkylideneaminyl radicals, so called iminyl radicals, and related reactions, see; S. Z. Zard, *Synlett*, **1996**, 1148.

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4 1,4-Dioxane is deoxygenated by bubbling with argon gas before use. When this operation was not performed, the yield of **2a** decreased to 68%.

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