

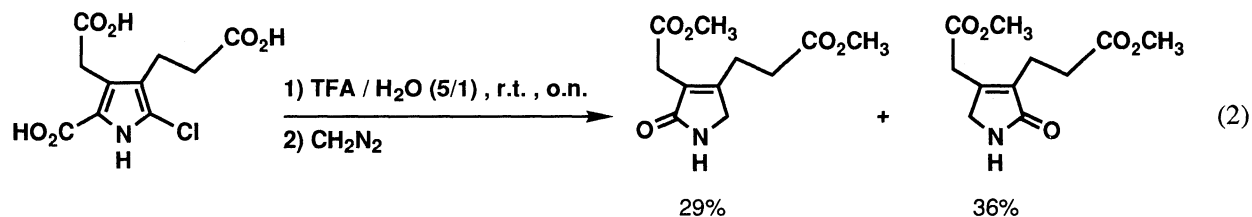
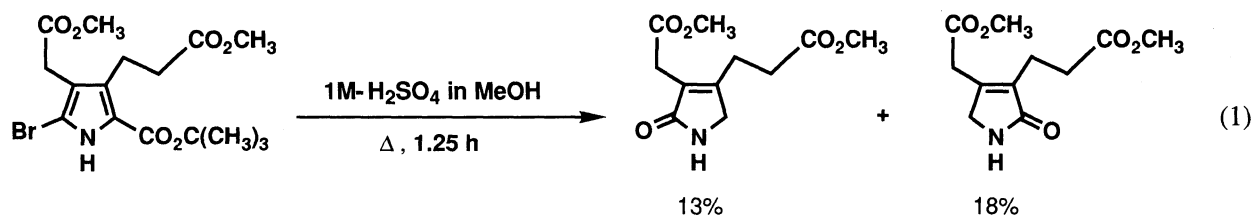
Convenient and Regioselective Syntheses of 3,4-Disubstituted Δ^3 -Pyrrolin-2-one Derivatives
Starting from 2-Tosyl-3,4-Disubstituted Pyrroles

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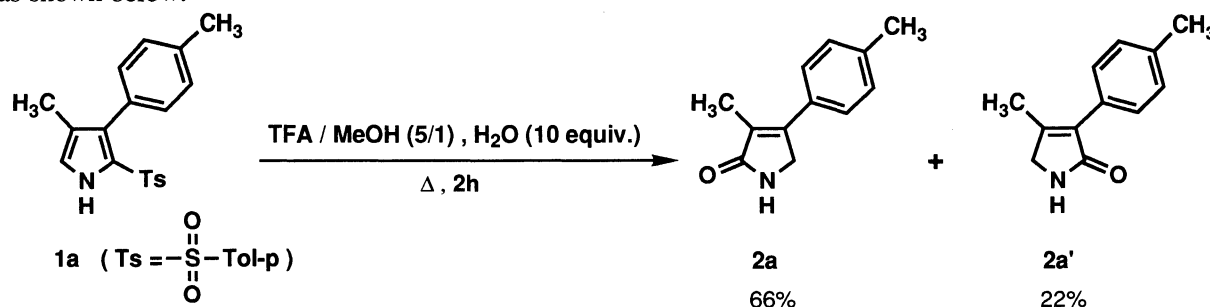
3,4-Disubstituted Δ^3 -pyrrolin-2-ones were prepared in high yields via 5-tosyl- Δ^3 -pyrrolin-2-ones (**4**) starting from 2-tosylpyrroles regioselectively. The compounds **4** were found to be useful intermediates for the preparation of a variety of Δ^3 -pyrrolin-2-one derivatives. The reactions of **4** with various nucleophiles and active methylene compounds bearing an appropriate leaving group are described.

The 3,4-disubstituted Δ^3 -pyrrolin-2-one derivatives are useful building blocks for the synthesis of biologically important substances such as the chlorins¹⁾ and the pigment component of phytochrome.²⁾ A variety of methods for the synthesis of Δ^3 -pyrrolin-2-one derivatives have been so far reported, for instance, the modification of the Paal-Knorr synthesis,^{3a)} intramolecular Horner-Emmons cyclization,^{3b)} condensation of acetoaminoketone with cyanoacetate,^{3c)} and reductive cyclization of the cyanohydrin derivatives of β -ketoester.^{3d)} In addition, direct structural transformation of substituted pyrroles to the corresponding Δ^3 -pyrrolin-2-ones has been also studied. For example, 2-formyl-3-ethyl-4-methylpyrrole was oxidized by hydrogen peroxide in pyridine to give Δ^3 -pyrrolin-2-ones concomitantly by the loss of the formyl group.⁴⁾ Acid hydrolysis of *t*-butyl 5-bromo-3(2-methoxycarbonyl-ethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate¹⁾ (Eq. 1) and 4-carboxyethyl-3-carboxymethyl-5-chloropyrrole-2-carboxylic acid⁵⁾ (Eq. 2) was investigated. However, neither chemical yield nor regioselectivity of them was satisfactory as shown in the following.

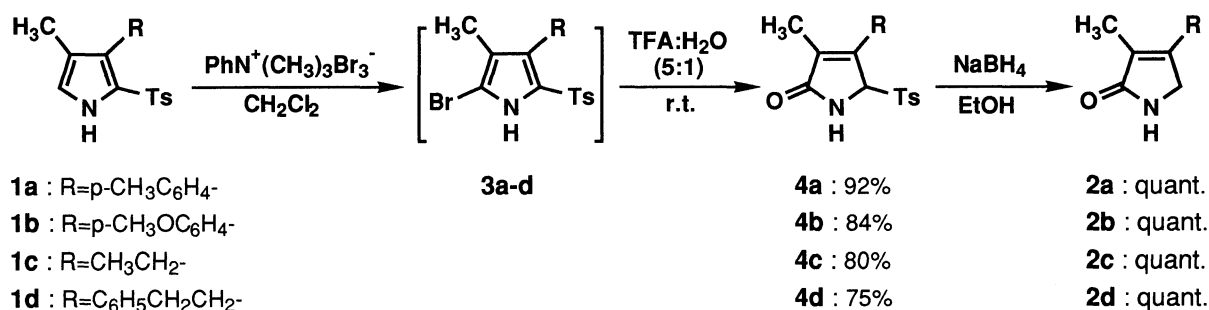


We wish to report here a versatile method for the regioselective syntheses of Δ^3 -pyrrolin-2-ones **2** via 3,4-disubstituted-5-(*p*-toluenesulfonyl=tosyl)- Δ^3 -pyrrolin-2-ones (**4**) starting from 2-tosyl-3,4-disubstituted pyrroles **1**, and the reactions of **4** with various nucleophiles and active methylene compounds bearing an appropriate leaving group. Compound **1** was chosen as a starting substance because of its ready availability⁶⁾ and strong inductive effect of the sulfonyl group which is expected to make selective protonation possible on the carbon of position 2.

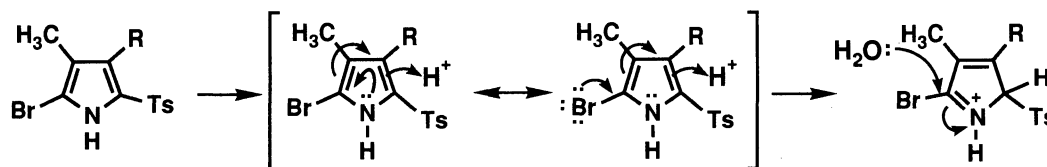
Actually, when **1a** was refluxed for 2 h in trifluoroacetic acid (TFA)-MeOH solution containing 10 equiv. of water, the desired product **2a** was obtained predominantly in good yield accompanied by the regioisomer **2a'** as shown below.

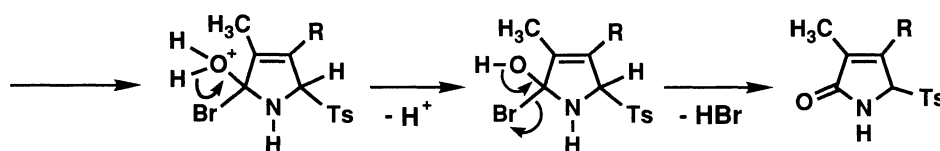


Formation of **2a'** seemed to be due to the competitive initial protonation on both carbons of positions 2 and 5. In order to improve the regioselectivity, **1a** was brominated with two equimolar amounts of trimethylphenylammonium tribromide in CH₂Cl₂ at 0 °C to afford **3a** in quantitative yield (Mp 199.0-201.5 °C from AcOEt-hexane). Then, to a solution of **3a** (100 mg, 0.25 mmol) in 5 ml of TFA was added 1 ml of water and the reaction mixture was allowed to stand overnight at room temperature with stirring. After usual work up and separation with a preparative TLC (SiO₂, hexane:AcOEt=1:1 V/V), only **4a** was obtained in 92% yield (79 mg, Mp 160.0-160.5 °C from *n*-PrOH). Next, **4a** (100 mg, 0.30 mmol) was treated with a small excess molar amounts of NaBH₄ in 5 ml of EtOH at room temperature for 5 min to provide **2a** in quantitative yield (56 mg, Mp 181.0-182.5 °C from AcOEt-hexane). Similarly, **1b-d** were transformed to **2b-d**⁷⁾ in high yields through **4b-d**⁷⁾ without purification of the intermediary **3b-d** as shown in the following scheme.



A plausible mechanism for regioselective hydrolysis of **3** toward **4** is shown below.





The facile reduction of **4** with NaBH_4 prompted us to examine the reaction of **4a** with various nucleophiles. Treatment of **4a** with a large excess amounts of aqueous methylamine provided the formal substitution product, 5-methylaminopyrrolinone **5a** in excellent yield (Run 1 in Table 1). It is most likely that the reaction proceeded through elimination and addition processes.⁸⁾ Similarly, **5b-f** were obtained under the reaction conditions described in Table 1.

Furthermore, the reaction of **4a** with the active methylene compound possessing a leaving group, such as methanesulfonyl(=Ms)-, benzenesulfonyl or tosyl(=Ts) group and bromide, was carried out in the presence of base. On treatment of **4a** with 1 molar amount of MsCH_2CN in the presence of 2.2 molar amounts of DBU(1,8-diazabicyclo[5.3.0]undec-7-ene), **6a** was obtained in high yield with predominance of Z-isomer through the substitution reaction followed by the elimination of methanesulfinic acid (Run 1 in Table 2). In the same way, the products **6b-d** were obtained. The results are listed in Table 2.

As mentioned above, a general method for the regioselective synthesis of 3,4-disubstituted- Δ^3 -pyrrolin-2-ones (**2**) could be established through 3,4-disubstituted 5-tosyl- Δ^3 -pyrrolin-2-ones (**4**) starting from 2-tosyl-3,4-disubstituted pyrroles (**1**), and it was found that the tosyl group of **4** is readily substituted by various nucleophiles affording **5** or exomethylene derivatives **6** in the case of active methylene compounds having a leaving group.

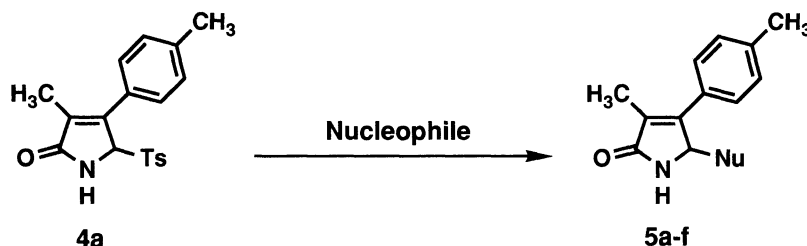
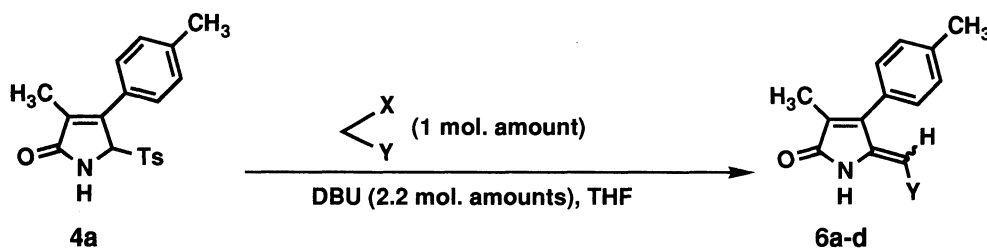


Table 1. The Reaction of **4a** with Various Nucleophiles

Run	Nucleophile (mol. amount)	Conditions (mol. amount)	Solvent	Product ^{a)}	Yield / %
1	NH_2CH_3 (20)	r.t., 30 min	$\text{CH}_3\text{CN} / \text{H}_2\text{O}$	5a	91 ^{b)}
2	$\text{NH}(\text{CH}_3)_2$ (20)	r.t., 5 min	$\text{CH}_3\text{CN} / \text{H}_2\text{O}$	5b	96 ^{c)}
3	CH_3OH (excess)	CH_3ONa (1.0), reflux, 5 min	CH_3OH	5c	quant. ^{d)}
4	NaSCH_3 (5.0)	r.t., 5 min	$\text{CH}_3\text{CN} / \text{H}_2\text{O}$	5d	85 ^{e)}
5	$\text{CH}_2(\text{CO}_2\text{CH}_3)_2$ (1.1)	CH_3ONa (2.2), reflux, 30 min	CH_3CN	5e	76 ^{f)}
6	$(\text{CH}_3)_2\text{CuMgBr}$ (2.0)	-10°C , 3 h	Et_2O	5f	45 ^{g)}
7	$(\text{CH}_3)_2\text{CuLi}$ (2.0)	-20°C –r.t., 1 h	Et_2O	5f	55

a) All the products gave the satisfactory spectral data. b) Mp 242.0 – 243.0°C (from AcOEt).
 c) Mp 155.0 – 156.0°C (from cyclohexane). d) Mp 134.5 – 135.0°C (from hexane).
 e) Mp 148.0 – 149.0°C (from AcOEt–hexane). f) Mp 144.0 – 144.5°C (from AcOEt–hexane).
 g) Mp 141.0 – 142.0°C (from cyclohexane).

Table 2. The Reaction of **4a** with Various Active Methylene Compounds

Run	X	Y	Conditions	Yield / %	Product ^{a)}	Ratio of Z / E isomers ^{b)}
1	CH ₃ SO ₂	CN	r.t., 0.5 h	75	6a	93 / 7 ^{c)}
2	CH ₃ SO ₂	CN	r.t., 3.5 h	83	6a	72 / 28
3	Ts	CN	r.t., on	74	6a	89 / 11
4	PhSO ₂	PhSO ₂	r.t., 0.5 h	53	6b	91 / 9 ^{d)}
5	Ts	CO ₂ Et	r.t., on	63	6c	96 / 4 ^{e)}
6	Br	CO ₂ Et	r.t., 1 h	54 ^{f)}	6c	97 / 3
7	Ts	COPh	r.t., 1 h	82	6d	72 / 28 ^{g)}

a) All the products gave the satisfactory spectral data. b) Stereochemistry of the products was determined by NOE measurement. c) Z-isomer; Mp 178.0-180.0 °C (from AcOEt-hexane), E-isomer; Mp 209.0-211.0 °C (from AcOEt-hexane). d) Z-isomer; Mp 152.0-153.0 °C (from EtOH). e) A mixture of E- and Z-isomers; Mp 81.0-82.0 °C (from hexane). f) 21% of ethyl p-toluenesulfonylacetate was produced. g) Z-isomer; Mp 178.0-179.0 °C (from benzene-hexane).

In the following paper, we report the Wittig type reaction of **4a** prepared in the present work with various aldehydes in the presence of PBu₃ and DBU affording the corresponding 5-exomethylene compounds in good yields.

References

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- 7) Melting points of **2b-d** and **4b-d** were shown in the following. **2b**: 163.0-164.0 °C (from n-PrOH); **2c**: 77.0-78.0 °C (from hexane); **2d**: 91.5-92.0 °C (from cyclohexane); **4b**: 158.0 °C (from n-PrOH); **4c**: 154.0-155.0 °C (from n-PrOH); **4d**: 174.5-175.0 °C (from n-PrOH).
- 8) D. S. Brown, P. Charreau, T. Hansson, and S. V. Ley, *Tetrahedron*, **47**, 1311 (1991); D. S. Brown, S. V. Ley, S. Vile, and M. Thompson *ibid.*, **47**, 1329 (1991); T. Kobayashi, N. Ishida, and T. Hiraoka., *J. Chem. Soc., Chem. Commun.*, **1980**, 736.

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