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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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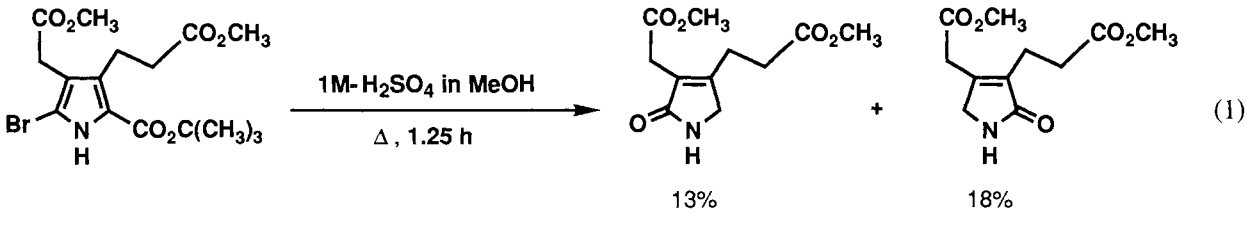
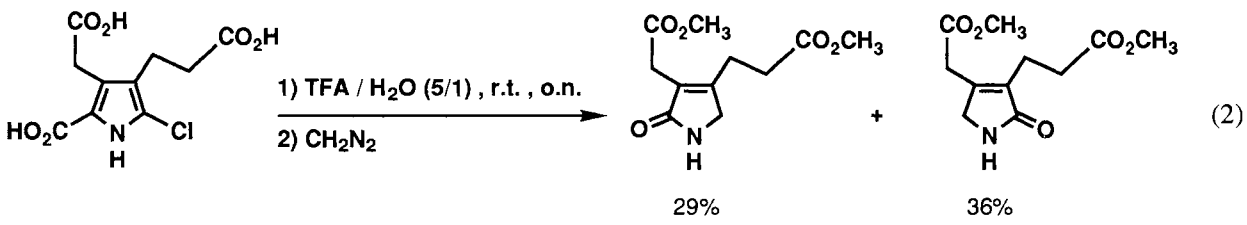
3,4-Disubstituted Δ^3-pyrrolin-2-ones were prepared in high yields via 5-tosyl-Δ^3-pyrrolin-2-ones (**4**) starting from 2-tosylpyrroles regioselectively. The compounds **4** were found to be useful intermediates for the preparation of a variety of Δ^3-pyrrolin-2-one derivatives. The reactions of **4** 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 chlorins[1] 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-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate[1] (Eq. 1) and 4-carboxyethyl-3-carboxymethyl-5-chloropyrrole-2-carboxylic acid[5] (Eq. 2) was investigated. However, neither chemical yield nor regioselectivity of them was satisfactory as shown in the following.



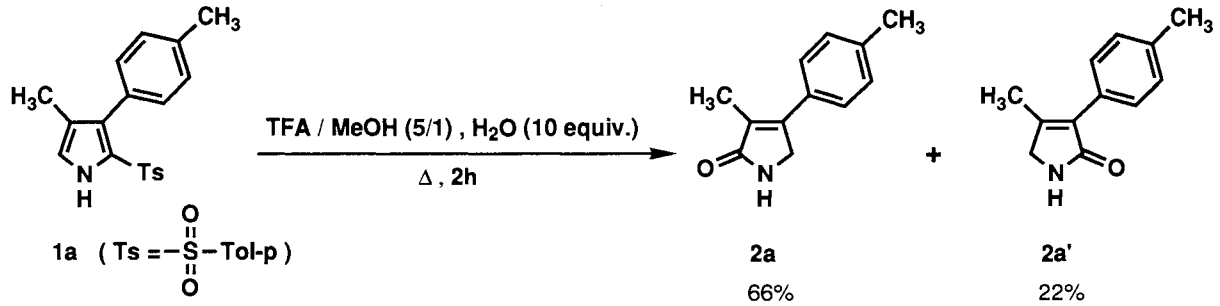
(1)



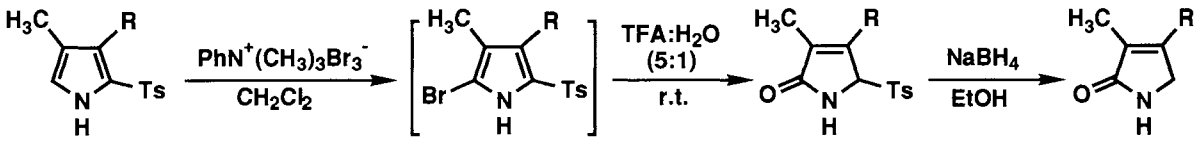
(2)

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 availability[6] 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.

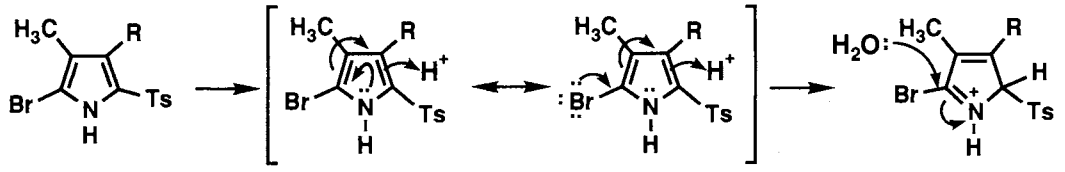


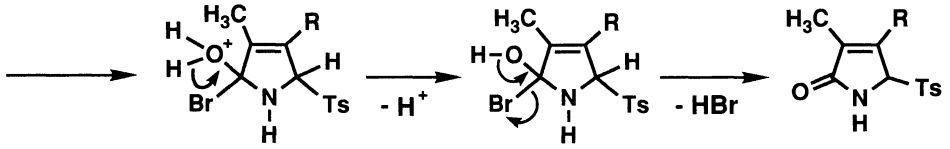
Formation of **2a'** seemed to be due to the competitive initial protonation on both carbons of positions 2 and 5. In order to improve the regioselectivity, **1a** was brominated with two equimolar amounts of trimethylphenylammonium tribromide in CH_2Cl_2 at 0 °C to afford **3a** in quantitative yield (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 (SiO_2, 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 $NaBH_4$ 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.



1a : R=p-$CH_3C_6H_4$-	**3a-d**	**4a** : 92%	**2a** : quant.
1b : R=p-$CH_3OC_6H_4$-		**4b** : 84%	**2b** : quant.
1c : R=CH_3CH_2-		**4c** : 80%	**2c** : quant.
1d : R=$C_6H_5CH_2CH_2$-		**4d** : 75%	**2d** : quant.

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

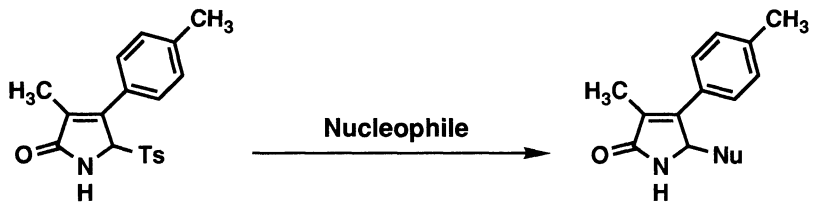




The facile reduction of **4** with $NaBH_4$ prompted us to examine the reaction of **4a** with various nucleophiles. Treatment of **4a** with a large excess amounts of aqueous methylamine provided the formal substitution product, 5-methylaminopyrrolinone **5a** in excellent yield (Run 1 in Table 1). 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-diazabicylo[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.

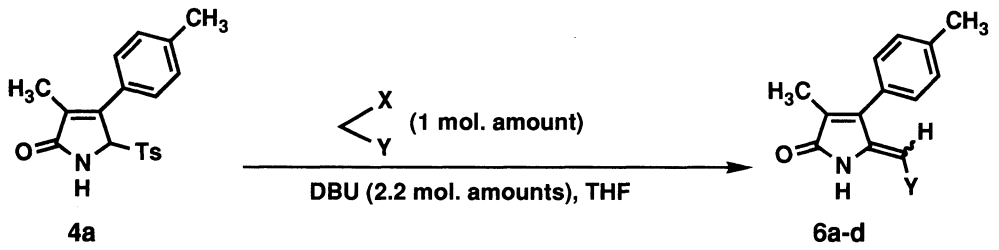


4a **5a-f**

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	CH_3CN / H_2O	**5a**	91[b]
2	$NH(CH_3)_2$ (20)		r.t., 5 min	CH_3CN / H_2O	**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	CH_3CN / H_2O	**5d**	85[e]
5	$CH_2(CO_2CH_3)_2$ (1.1)	CH_3ONa (2.2),	reflux, 30 min	CH_3CN	**5e**	76[f]
6	$(CH_3)_2CuMgBr$ (2.0)		-10 °C, 3 h	Et_2O	**5f**	45[g]
7	$(CH_3)_2CuLi$ (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).



4a **6a-d**

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_3SO_2	CN	r.t., 0.5 h	75	**6a**	93 /7[c]
2	CH_3SO_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_2Et	r.t., on	63	**6c**	96 / 4[e]
6	Br	CO_2Et	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-toluenesulfonyl-acetate 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 PBu_3 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).

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