Rearrangement of Tosyl Group of 3,4-Disubstituted 2-Tosylpyrroles under Mild Acidic Conditions

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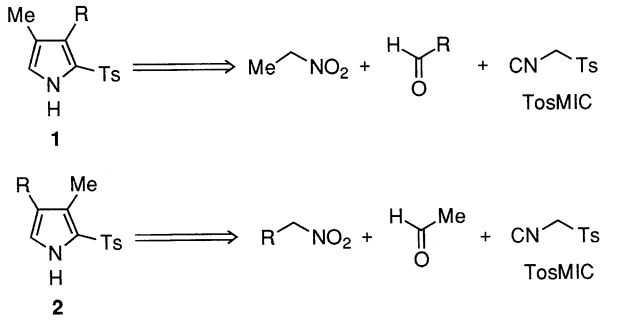
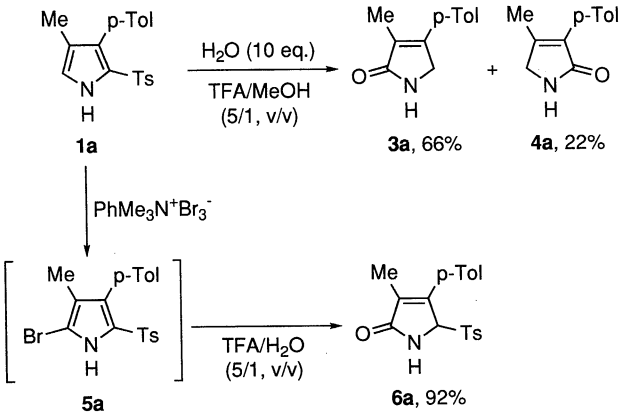
Tosyl group of 3,4-disubstituted 2-tosylpyrroles easily rearranged from 2- to 5-position by treatment with TFA. The ratio of the regioisomers at equilibrium was definitely influenced by the bulkiness of the substituent at 3-position of the starting 2-tosylpyrroles.

Barton and his co-workers reported a convenient method for the preparation of substituted pyrrole derivatives via the reaction of isonitrile with nitroolefin or its equivalent obtained from nitroalkane and aldehyde.[1] However, we were sometimes confronted with the difficulty to introduce arbitrary substituents to 3- and 4-positions according to the method. Namely, for example, synthesis of 4-methyl-3-substituted 2-tosylpyrrole (**1**) is much easier than that of 3-methyl-4-substituted 2-tosylpyrrole (**2**) which is a regioisomer of (**1**), because the substituent of 3-position of the former is originated from aldehydes many of which are commercially available and that of 4-position of the latter is from nitro compounds which are not so easy to obtain (Scheme 1).

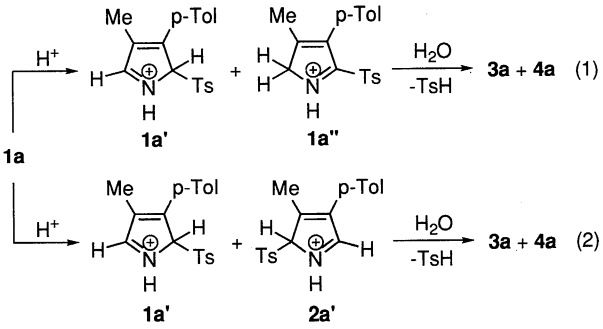


Scheme 1.



Scheme 2.

Recently, we have reported a convenient method for the preparation of 3,4-disubstituted 2-tosylpyrrole derivatives and their regioselective transformation to the corresponding pyrrolinone derivatives (Scheme 2),[2] which are useful building blocks for the preparation of pyrromethenone derivatives related to C/D-ring component of the tetrapyrrole bile pigments like phytochromobilin and phycocyanobilin.[3] Acidic hydrolysis of 2-tosylpyrrole derivative (**1a**) gave a mixture of two pyrrolinone derivatives being regioisomers (**3a, 4a**), while that of 2-bromo-5-tosylpyrrole derivative (**5a**) gave a single isomer (**6a**).



The formation of **3a** and **4a** from **1a** suggested two possible pathways, namely, (1) initial protonation occurred at both 2- and 5-positions of **1a** to give **1a'** and **1a"**, followed by hydrolysis resulted in the formation of **3a** and **4a** (eq. 1), or (2) protonation occurred only at 2-position of **1a** and tosyl group subsequently rearranged prior to the hydrolysis through **1a'** and **2a'** (eq. 2).

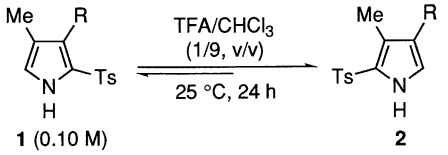


Table 1.

Run	**1a-e**,	R	Isolated Yield **2+1** / %	**2** / **1**[a]
1	**1b**,	$PhCH_2CH_2$-	98	59 / 41
2	**1b**,	$PhCH_2CH_2$-	95[b]	72 / 28
3	**1c**,	Et-	92	73 / 27
4	**1d**,	i-Pr-	94	89 / 11
5	**1a**,	p-Tol-	99	94 / 6
6	**1e**,	t-Bu-	92	100 / 0

a The ratios were determined by 400 MHz ^{1}H NMR.

b Reacted for 48 h.

The latter consideration prompted us to treat 4-methyl-3-substituted 2-tosylpyrroles (**1a-e**)[4] with an acid without water. Ultimately, it was found that tosyl group of **1** quite readily rearranged from 2- to 5-position with trifluoroacetic acid (TFA)[5] as shown in Table 1. The ratio of the regioisomers at equilibrium was influenced by the bulkiness of the substituent at 3-position of the starting 2-tosylpyrroles. When the substituent R is t-butyl group, **1e** was completely transformed to **2e** (Table 1, Run 6).

Time-course of the rearrangement of tosyl group of **1** was observed by NMR spectrum as illustrated in Figure 1. From these results, it was found that the rearrangement reaction reaches equilibrium in about 30 h except for the case of **1e** (R = t-Bu), where it completed within 30 min.

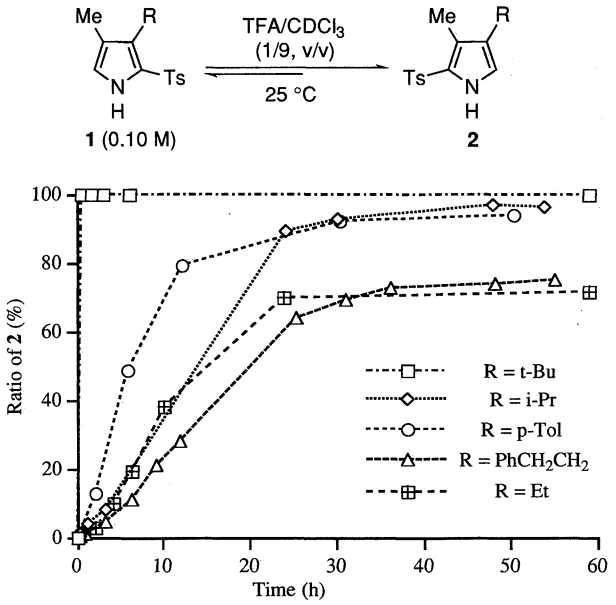
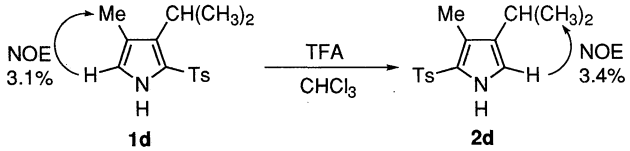


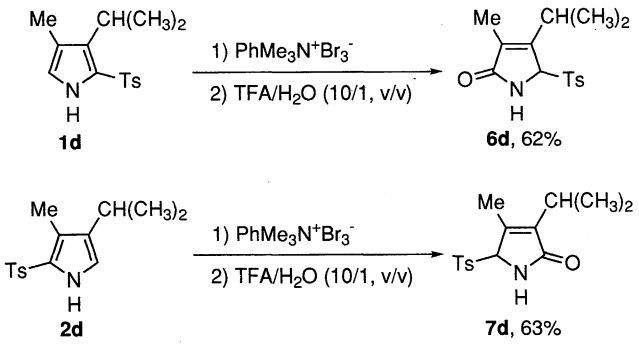
Figure 1. Time-course of the rearrangement of tosyl group.

The resulting rearrangement products (**2**) are isolable by recrystallization[6], since all of the tosylpyrroles are well crystalline compounds. Therefore, it is obviously possible to transform almost all of the 3,4-disubstituted 2-tosylpyrroles to the corresponding regioisomers by repeating the present rearrangement and recrystallization.



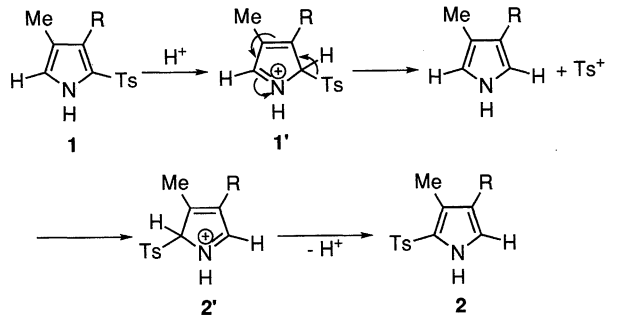
Scheme 3.

Structure of **2** was confirmed by NOE measurement (Scheme 3), and the obtained two regioisomers (**1d**, **2d**) were converted to the corresponding tosylpyrrolinones (**6d**, **7d**), respectively, according to our original method[2] (Scheme 4).



Scheme 4.

Although the precise mechanism for this rearrangement is not clear, a possible mechanism is shown in the following.



In conclusion, we could have found a noble reaction that the tosyl group of the 2-tosylpyrrole derivatives rearranges from 2- to 5-position under mild acidic conditions, which provide a very convenient method for the preparation of both regioisomers of 2-tosylpyrroles, and it was revealed that the ratio of the isomers at equilibrium is influenced by the bulkiness of the substituent at 3-position of the starting 2-tosylpyrroles.

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References and Notes

1 D. H. R. Barton, J. Kervagoret, and S. Z. Zard, *Tetrahedron*, **46**, 7587 (1990).
2 H. Kinoshita, Y. Hayashi, Y. Murata, and K. Inomata, *Chem. Lett.*, **1993**, 1437.
3 H. Kinoshita, Hla Ngwe, K. Kohori, and K. Inomata, *Chem. Lett.*, **1993**, 1441; K. Kohori, M. Hashimoto, H. Kinoshita, and K. Inomata, *Bull. Chem. Soc. Jpn.*, **67**, 3088 (1994).
4 The tosyl pyrroles were prepared from TosMIC and nitroolefin (for **1a**) or β-(acetoxy)nitroalkane (for **1b-e**), respectively, in the yields as follows; **1a** = 82%, **1b** = 86%, **1c** = 83%, **1d** = 91 %, **1e** = 78%.
5 When acetic acid or formic acid was used, no rearrangement occurred under the similar reaction conditions, and methanesulfonic acid gave the complicated mixture.
6 After recrystallization of the mixture from 2-propanol, each **2** was isolated in the yield as follows; **2a** = 76%, **2b** = 53%, **2d** = 42 %, **2e** = 60%.