NEW [1,2] REARRANGEMENT OF *p*-TOLUENESULFONYL GROUP IN AZOLES BY n-BUTYLLITHIUM

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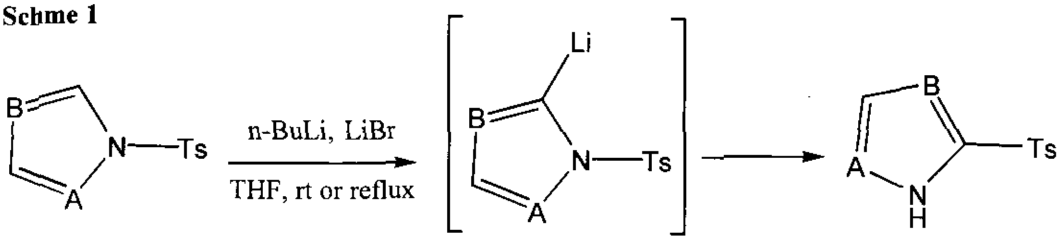
Abstract - A new type of [1,2] rearrangements of toluenesulfonyl group from nitrogen to neighboring carbon atom by n-butyllithium in tetrahydrofuran has been achieved in azoles, where the addition of lithium bromide accelerated the reaction in good yields.

The rearrangements of sulfonyl group in heterocyclic compounds have been studied in various ways.[1,2] *N*-Sulfonyl anilides suffer [1,3] or [1,5] shifts of sulfonyl group under various reaction conditions,[3,4] To the best of our knowledge, *[1,2] shifts of sulfonyl group of N-sulfonyl heterocycles have not been studied yet.* In case of the *N*-sulfonylated azoles, the *p*-toluenesulfonyl group was used as a protecting group which induced direct 2-metallation by its ability to stabilize neighboring cabanion, and could introduce 2-substituents by various electrophiles.[5] When *N*-*p*-toluenesulfonylimidazole was lithiated by n-butyllithium, we have found the *p*-toluenesulfonyl group rearranged smoothly to the next carbon atom by raising the reaction temperature and increasing the reaction time.

Herein we wish to report our results on the [1,2] rearrangement of sulfonyl group in various *N*-sulfonyl azoles, which is thought to be very important not only in the basic aspect but also in the synthetic one (Scheme 1).

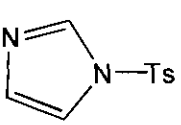
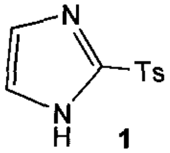
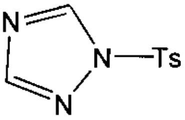
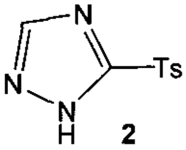
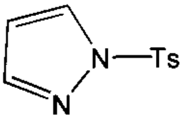
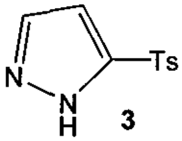
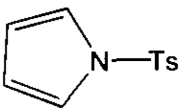
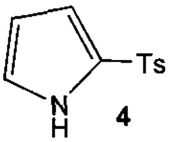
N-*p*-Toluenesulfonylations[7, 8] of the 1,2,4-triazole, imidazole, pyrazole, and pyrrole were performed by the reaction of *p*-toluenesulfonyl chloride and a base, and the *N*-*p*-toluenesulfonyl heterocycles were purified by a silica gel chromatography or by recrystallization. The *N*-*p*-toluenesulfonyl heterocycles were dissolved in anhydrous tetrahydrofuran, cooled to -78 °C and 1.2 equiv of n-butyllithium was added. The reaction mixture was heated under reflux until the reaction became complete. The rearranged product was easily separable by silica gel column chromatography. The results are summarized in Table 1.[9]

Schme 1



A, or B = N,or CH

Table 1. Rearrangement of *p*-Toluenesulfonyl Group in Azoles

Entry	Reactant	Product	Reaction Conditions[a]	Additive[b]	Yield (%)
1		 **1**	reflux 12 h	none	55
2			reflux 5 h	LiBr	87
3		 **2**	rt 12 h	none	88
4			rt 3 h	LiBr	96
5		 **3**	reflux 36 h	none	57
6			reflux 12 h	LiBr	71
7		 **4**	reflux 24 h	none	16
8			reflux 24 h	LiBr	53

a) Reaction solvent: THF

b) none: only 1.6 M n-BuLi of Aldrich Co. LiBr: 1 eq of LiBr

Especially, *N*-*p*-toluenesulfonyltriazole was easily rearranged even at room temperature to afford **2** in good yield (Entries 3 and 4), whereas the others were required more vigorous reaction conditions with longer reaction time.[6] It is noteworthy that the addition of lithium bromide accelerated the migration with improved yields. The effect of the addition of lithium bromide in these cases can hardly be explained but we could speculate lithium bromide might change the aggregation states of the carbanion.[9]

All of the rearranged products were easily distinguished from the starting materials by the ^{1}H NMR spectra. 3(5)-*p*-Toluenesulfonylpyrazole (**3**)[10] showed two doublets at 8.05 and 6.80 ppm for the corresponding 3-H and 4-H, while 2-*p*-toluenesulfonylimidazole (**1**) showed a singlet at 7.18 ppm for the symmetric 4-H and 5-H. For the rearranged product from *N*-*p*-toluenesulfonylpyrrole, we confirmed the product as 2-*p*-toluenesulfonylpyrrole (**4**) by comparison of ^{1}H-NMR spectra of 2- and 3-benzenesulfonyl pyrroles.[2a]

In conclusion, novel [1,2] rearrangements of toluenesulfonyl group from nitrogen to neighboring carbon atom in azoles were achieved by n-butyllithium and the addition of lithium bromide can accelerate the rearrangement to afford the products in good yields.

EXPERIMENTAL SECTION

Melting points were measured in capillary tubes with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H-NMR spectra were obtained with a Varian GEMINI-200. All chemical shifts are reported in ppm downfield from internal tetramethylsilane and coupling constants are given in Hz. Mass spectra were obtained on a Shimadzu GCMS-QP 1000 mass spectrometer. Chromatographic separations were carried out on a silica gel column (Merck silica gel 60).

2-Toluensulfonylimidazole (1)

To a stirred solution of *N*-toluenesulfonylimidazole (0.5 g, 2.3 mmol) and dried LiBr (0.2 g, 2.3 mmol) in THF (10 mL) at -70 °C was added slowly n-BuLi (1.2 mL of 2.2 M, 2.64 mmol). The reaction mixture was allowed to stand at rt and subsequently refluxed for 5 h. After cooling with an ice-bath, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, and then, extrated with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, evaporated, and the crude material was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 1/1) to offer the corresponding product (**1**) (0.44 g, 87 %) as colorless solid. mp 182-184°. ^{1}H NMR (200 MHz, MeOH-d_4) δ 7.81 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.18 (s, 2H), 2.33 (s, 3H); IR (cm^{-1}, KBr) 3412 (NH), 1329, 1107 (SO_2); MS (70 eV) m/z (rel. intensity) 158 (100), 222 (M^+, 12), 223 (M^++1, 5) . *Anal.* Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.88; H, 4.25; N, 12.87.

3-Toluensulfonyltriazole (2)

To a stirred solution of *N*-toluenesulfonyltriazole (0.5 g, 2.2 mmol) and dried LiBr (0.19 g, 2.2 mmol) in THF (10 mL) at -70 °C was added slowly n-BuLi (1.2 mL of 2.2 M, 2.64 mmol). The reaction mixture was allowed to stand at rt for 3 h. After cooling with an ice-bath, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, and then, extrated with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, evaporated, and the crude material was purified by silica gel chromatography (dichloromethane/ethyl acetate = 1/1) to offer the corresponding product (**2**) (0.44 g, 96 %) as colorless solid. mp 195-197° (ether). ^{1}H NMR (200 MHz, MeOH-d_4) δ 8.62 (s, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H); IR (cm^{-1}, KBr) 3151 (NH), 1336, 1150 (SO_2); MS (70eV) m/z (rel. intensity) 223 (M^+, 12), 224 (M^++1, 4); *Anal.* Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.39; H, 4.23; N, 18.98.

3(5)-Toluensulfonylpyrazole (3)[10]

To a stirred solution of *N*-toluenesulfonylpyrazole (0.5 g, 2.3 mmol) and dried LiBr (0.2 g, 2.3 mmol) in THF (10 mL) at -70 °C was added slowly n-BuLi (1.2 mL of 2.2 M, 2.64 mmol). The reaction mixture was allowed to stand at rt and subsequently refluxed for 12 h. After cooling with an ice-bath, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, and then, extrated with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, evaporated, and the crude material was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 1/1) to offer the corresponding product (**3**) (0.36 g, 71 %) as colorless solid. mp 156-157°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 14.05 (br s, 1H, D_2O exchangeable), 8.05 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.28 (d, J=8.2 Hz, 2H), 6.80 (d, J=2.4 Hz, 1H), 2.33 (s, 3H); IR (cm^{-1}, KBr) 3314 (NH), 1319, 1142 (SO_2); MS (70eV) m/z (rel. intensity) 91 (100), 149 (71), 222 (M^+, 19), 223 (M^++1, 5); *Anal.* Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.31; H, 4.27; N, 12.76.

2-Toluensulfonylpyrrole (4):

To a stirred solution of *N*-toluenesulfonylpyrrole (0.5 g, 2.3 mmol) and dried LiBr (0.2 g, 2.3 mmol) in THF (10 mL) at -70 °C was added slowly n-BuLi (1.2 mL of 2.2 M, 2.64 mmol). The reaction mixture was allowed to stand at rt and subsequently refluxed for 24 h. After cooling with an ice-bath, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, and then, extrated with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, evaporated, and the crude material was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 3/1) to offer the corresponding product (**4**) (0.27 g, 53 %) as colorless solid. mp 160-162°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.38 (br s, 1H, D_2O exchangeable), 7.90 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 6.97 (m, 1H), 6.85 (m, 1H), 6.30 (m, 1H), 2.31 (s, 3H); IR (cm^{-1}, KBr) 3320 (NH), 1320, 1141 (SO_2); MS (70 eV) m/z (rel. intensity) 156 (39), 221 (M^+, 100), 222 (M^++1, 11); *Anal.* Calcd for $C_{11}H_{11}NO_2S$: C, 59.70; H, 5.01; N, 6.33. Found: C, 59.97; H, 4.95; N, 6.08.

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10. It has been known that the *N*-unsubstituted pyrazoles in solution are mixtures of tautomers in different proportions, depending on the nature of the substituents and solvents, see: J. Elguero, 'Comprehensive Heterocyclic Chemistry,' ed. by K. T. Potts, Pergamon Press, Oxford, 1984, pp.167-303, and the references cited therein. We did not established if compound **(3)** is 3- or 5-toluensulfonylpyrazole, or an equilibrium mixture of the two isomers.

Received, 8th September, 1997