CHEMISTRY LETTERS, pp. 1033-1036, 1986.

A NEW AND EFFECTIVE AMINOMETHYLATION BY THE USE OF N-(p-TOLUENESULFONYLMETHYL)-p-TOLUENESULFONAMIDE AS AN EQUIVALENT OF METHANIMINE. A CONVENIENT PREPARATION OF PYRROLE COMPOUNDS

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Readily available N-(p-toluenesulfonylmethyl)-p-toluenesulfonamide was treated with base to generate N-methylene-p-toluenesulfonamide which reacted with a variety of nucleophiles forming the corresponding N-tosyl-aminomethylated compounds in good yields. Furthermore, the N-tosyl-aminomethylated acetals thus obtained were converted into the corresponding N-tosylpyrroles with the aid of acid catalyst in excellent yields.

Useful aminomethylating agents such as Mannich base and Eschenmoser's salt[1] have been widely employed in synthetic chemistry, for instance, to introduce carbon-carbon double bond.

We now wish to report that N-(p-toluenesulfonylmethyl)-p-toluenesulfonamide (1)[2] readily derived from p-toluenesulfonamide ($TsNH_2$), formalin, and sodium p-toluenesulfinate·$4H_2O$ ($TsNa·4H_2O$) in formic acid[3] is a very versatile reagent for aminomethylation. Treatment of 1 with suitable base resulted in effective elimination of p-toluenesulfinic acid (TsH) to give labile N-methylene-p-toluene-sulfonamide (2) which reacted with a variety of nucleophiles to afford the corresponding N-tosyl-aminomethylated compounds 3 in good yields as shown in Eq. 1.

$$\underset{1}{TsNHCH_2Ts} \xrightarrow[[-TsH]]{\text{Base}} \underset{2}{[CH_2{=}N\text{-}Ts]} \xrightarrow[2)\ H^{\oplus}]{1)\ :Nu^{\ominus}} \underset{3}{NuCH_2NHTs} \qquad (1)$$

At first, a solution of 1 in THF was added dropwise to a solution of N-(1-cyclohexenyl)pyrrolidine and 1.1 equiv. of DBU in THF at 0 °C for 20 min. After

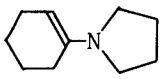
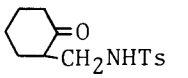
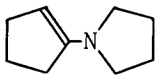
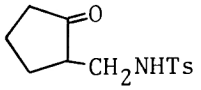
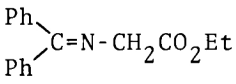
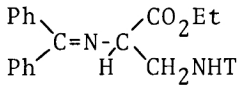
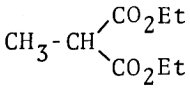
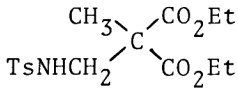
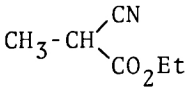
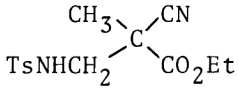
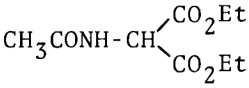
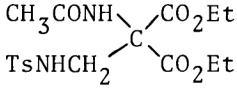
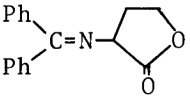
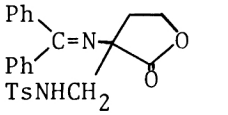
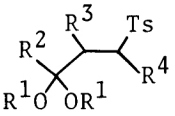
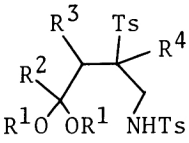
vigorous stirring at room temperature for 2 h and acid hydrolysis, 2-(N-tosyl aminomethyl)cyclohexanone (3a) was obtained in 65% yield (Entry 1). A similar reaction with N-(1-cyclopentenyl)pyrrolidine gave 3b in a poor yield (Entry 2).

Next, the reaction of 1 with several ester-stabilized carbanions was tested. To a solution of ethyl N-(diphenylmethylene)glycinate[4] (77 mg, 0.25 mmol) and 2.5 equiv. of DBU (95 mg, 0.63 mmol) in THF (2 ml) was added a solution of 1.5 equiv. of 1 (124 mg, 0.37 mmol) in THF (10 ml) using mechanically driven syringe in a period of 3 h at room temperature. Then, the reaction mixture was stirred for additional 1 h. After usual work-up and separation with a preparative TLC (SiO_2, hexane:AcOEt=1:1 v/v), 3c was obtained in 71% yield (80 mg). A similar reaction with diethyl malonate gave no trace of diethyl N-tosylaminomethylmalonate, but, diethyl bis(N-tosylaminomethyl)malonate, diethyl 2,4-diethoxycarbonyl-2-(N-tosyl-aminomethyl)glutamate, and $TsNH_2$ were obtained in 16%, 14%, and 45%, respectively. In the light of the above result, diethyl methylmalonate was treated with 1 under the same reaction conditions as Entry 3 to give the desired product 3d in 83% yield. Similarly, compounds 3e-g were prepared in good yields as shown in Table 1.

Subsequently, the reaction of 1 with the carbanion of sulfone compounds was investigated under various conditions. The following procedure was found most suitable for the preparation of 3h-n: After the addition of MeLi (1.7 M in ether, 0.24 ml, 0.40 mmol) to a vigorously stirred solution of 1 (133 mg, 0.40 mmol) in THF (23 ml) at - 100 °C under N_2, a solution of the lithium salt prepared in another flask from the reaction of β-benzyl-β-tosylpropanal dimethyl acetal (40 mg, 0.115 mmol) with 1.1 equiv. of BuLi in THF (2 ml) at -78 °C for 1 h under N_2 was added. The reaction mixture was warmed to -78 °C and worked up in the usual way. β-N-Tosylaminomethylated propanal 3h was isolated in 76% yield. In a similar way, compounds 3i-n were prepared in good yields (Entries 9-14).

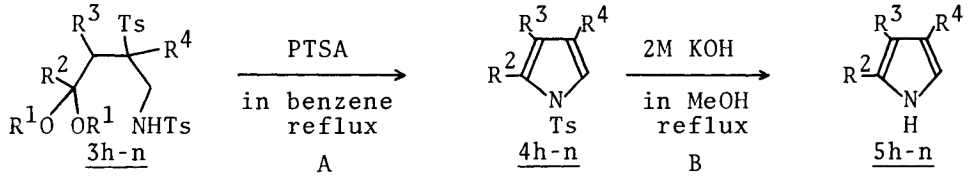
In the previous papers,[5] we have reported that γ-hydroxy-β-tosylbutanal acetals were converted into furans effectively by means of acid catalyst. Therefore, compound 3h thus prepared was allowed to reflux in benzene for 15 min in the presence of a catalytic amount of p-toluenesulfonic acid (PTSA) under N_2. After separation by a preparative TLC (SiO_2, benzene:AcOEt=90:1 v/v), N-tosyl-3-benzylpyrrole (4h) was obtained in 80% yield. Similarly, compounds 4i-n were

Table 1. Reaction of N-Tosylaminomethylating Agent 1 with Various Nucleophiles

Entry	Substrate	Molar ratio of base[b]/1/substrate	Product[a] (3a-n)	Yield/%
1		1.1/1/1	 3a[c]	65[d]
2		1.1/1/1	 3b[e]	24
3		2.5/1.5/1	 3c[f]	71
4		2.8/1.5/1	 3d[e]	83
5		2.8/1.5/1	 3e[g]	82
6		2.8/1.5/1	 3f[e]	94
7		2.8/1.5/1	 3g[h]	74
				
	R^1 R^2 R^3 R^4		(3h-n)	
8	CH_3 H H $PhCH_2$	3.5/3.5/1	3h[i]	76
9	CH_3 H H $PhCH_2CH_2$	3.5/3.5/1	3i[j]	74
10	CH_3 H H $CH_3(CH_2)_{10}$	3.5/3.5/1	3j[e]	59
11	$-(CH_2)_2-$ CH_3 H $PhCH_2$	3.5/3.5/1	3k[k]	82
12	$-(CH_2)_2-$ CH_3 H $PhCH_2CH_2$	3.85/3.5/1	3l[m]	71
13	$-(CH_2)_2-$ CH_3 H CH_3CH_2	3.85/3.5/1	3m[e]	71
14	$-(CH_2)_2-$ H CH_3 CH_3CH_2	3.85/3.5/1	3n[e,n]	58

a) All compounds gave satisfactory spectral data. b) DBU in Entries 1-7 and MeLi in Entries 8-14 were used as bases. c) Mp 84-86 °C (from benzene-hexane). d) 2,6-Bis(N-tosylaminomethyl)cyclohexanone was obtained in 9% yield besides 3a. e) Obtained as an oily product. f) Mp 106-107 °C (from ether). g) Mp 105.5-107 °C (from ether). h) Mp 169.5-171 °C (from ether). i) Mp 98.5-99.0 °C (from n-PrOH). j) Mp 103-103.5 °C (from n-PrOH). k) Mp 91-92 °C (from n-PrOH). m) Mp 96.5-97.5 °C (from EtOH). n) Obtained as mixture of diastereoisomers (78:22).

Table 2. Conversion of N-Tosylaminomethylated Acetal Derivatives into Pyrroles



3h-n 4h-n 5h-n

	Starting material				Reaction time		Yield/%	
	R^1	R^2	R^3	R^4	A	B	4h-n[a]	5h-n[a,b]
3h	CH_3	H	H	$PhCH_2$	15 min	2 h	80[c]	quant.
3i	CH_3	H	H	$PhCH_2CH_2$	5 min	2.5 h	83[d]	quant.
3j	CH_3	H	H	$CH_3(CH_2)_{10}$	5 min	2 h	quant.[b]	quant.
3k	$-(CH_2)_2-$	CH_3	H	$PhCH_2$	5 min	2 h	quant.[b]	quant.
3l	$-(CH_2)_2-$	CH_3	H	$PhCH_2CH_2$	10 min	6.5 h	94[b]	92
3m	$-(CH_2)_2-$	CH_3	H	CH_3CH_2	10 min	6.5 h	80[b]	88
3n	$-(CH_2)_2-$	H	CH_3	CH_3CH_2	10 min	4 h	quant.[e]	94

a) All compounds gave satisfactory spectral data. b) Obtained as an oily product. c) Mp 91.5-92.0 °C (from hexane). d) Mp 93.5-94.0 °C (from heptane). e) Mp 52.5-53.0 °C (from hexane).

prepared in high yields as shown in Table 2. On treatment of 4h-n with 2 M KOH in refluxing MeOH,[6] detosylation reaction proceeded very smoothly to afford 5h-n in quantitative yields as shown in Table 2.

As mentioned above, the readily available compound 1 proved to be a very useful reagent for aminomethylation.

Further studies on the scope and limitation of this reagent 1 in organic synthesis are now undergoing.

References

1) J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, Angew. Chem., Int. Ed. Engl., 10, 330(1971).
2) The reagent 1 was prepared as follows: A solution of $TsNH_2$ (855 mg, 5 mmol), $TsNa \cdot 4H_2O$ (1.25 g, 5 mmol), and 0.5 ml of formalin in 1 ml of HCO_2H and 5 ml of H_2O was warmed at 80 °C for 2 h. Recrystallization from EtOH gave pure 1 in 86% yield (Mp 163-163.5 °C). Found: C, 53.02; H, 5.06; N, 4.07%. Calcd for $C_{15}H_{17}NO_4S_2$: C, 53.08; H, 5.05; N, 4.13%.
3) A. M. Van. Leusen and J. Strating, Org. Synth., 57, 95(1977).
4) M. J. O'Donnell and R. L. Polt, J. Org. Chem., 47, 2663(1982).
5) H. Kotake, K. Inomata, H. Kinoshita, S. Aoyama, and Y. Sakamoto, Heterocycles, 10, 105(1978), K. Inomata, Y. Nakayama, M. Tsutsumi, and H. Kotake, ibid., 12, 1467(1980).
6) W. G. Terry, A. H. Jackson, G. W. Kenner, and G. Kornis, J. Chem. Soc., 1965, 4389.

(Received March 31, 1986)