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Fluxional sulfonyl derivatives of troponoids and colchicinoids

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Abstract—In what represents the first examples of fluxional sulfonyl derivatives, the tosyl group in the couple 4-isopropyltropone/6-isopropyltropone (**3**/**4**), the tosyl or mesyl groups in the couple colchicine/isocolchicine (**5**/**6** or **7**/**8**), and the tosyl group in the couples of colchicinoids **9**/**10** and **11**/**12**, were observed to undergo thermally-induced shift between the two tropolone-like oxygen atoms, likely via a bipyramidal intermediate; recycling of tosylates or mesylates of biologically inactive isocolchicinoids into the corresponding tosylates or mesylates of biologically active colchicinoids affords synthetic value to the unselective tosylation or mesylation of colchiceine.

In 2-acetoxytropone (**1a**) and analogues, migration of the acyl group via intramolecular attack at the carbonyl carbon by the cycloheptatrienone carbonyl oxygen proceeds very rapidly even at low temperatures, as indicated by a marked temperature dependence of their ^{1}H NMR and ^{13}C NMR spectra in the 203–298 K range.[1]

In contrast with the acetyl group, the tosyl group has never been described to impart fluxional behavior to suitable systems to which it is bound, such as the troponoids, e.g. 2-tosyloxytropone (**2a**).[2] Therefore, it is interesting to have observed, and report here, fluxional behavior for tosylates and mesylates of both troponoids and colchicinoids, albeit under forcing conditions. Thus, the tosylate of β-thujaplicine (2-tosyloxy-4-isopropyltropone, **3**)[3] in DMF at 100°C in about 2.5 h was observed to change into a 1:0.9 mixture with 2-tosyloxy-6-isopropyltropone (**4**)[3] (Chart 1). That this is an equilibrium mixture was proven by isolating pure **4** and subjecting it to a similar procedure, by which the same 1:0.9 mixture of **3** and **4** was obtained. Similar observations were made with either the tosylates (**5**/**6**)[4] and the mesylates (**7**/**8**)[5] in the colchicine/isocolchicine system, and with tosylates in the neocolchicine/pseudocolchicine and 5,6-didehydro-7-deacetamidocolchicine/5,6-didehydro-7-deacetamidoisocolchicine systems (**9**/**10**[6] and **11**/**12**[7] respectively) (Chart 2). In the equilibrium mixtures of compounds obtained on heating pure compounds in the 100–140°C temperature range, the prevailing isomer (by about 2.4:1) bears a double bond between C7a and C12a.

1a X=OAc, Y=Z=H **1b** X=OAc, Y=Z=H
2a X=OTs, Y=Z=H **2b** X=OTs, Y=Z=H
3 X=OTs, Y= ^{i}Pr, Z=H **4** X=OTs, Y=^{i}Pr, Z=H

Chart 1.

The equilibrium processes (for which rate coefficients are given in Table 1) could be disentangled into forward and backward reaction on the basis of the equilibrium position. The activation parameters, determined in the 100–140°C temperature range (Table 2), are similar for all fluxional processes examined,[8] the largest deviation being observed for the mesylates of the colchicine/isocolchicine system (**7**/**8**), which show a slightly higher enthalpy of activation, for both the forward and the backward reaction, than the other sulfonates.

The data in Table 2 show that fluxionality with tosyl group is typified by about 2.5 fold higher activation energy than the acyl group, evaluated as about 11 kcal mol^{-1} for **1a**.[1] The NMR spectra of the above tosylates are therefore temperature independent in the normally accessible range, which explains why these fluxional processes have passed unnoticed with systems such as **2a**/**2b** which give undistinguishable isomers.

Keywords: colchicinoids; troponoids; tosylates; mesylates; tosyl or mesyl migration.

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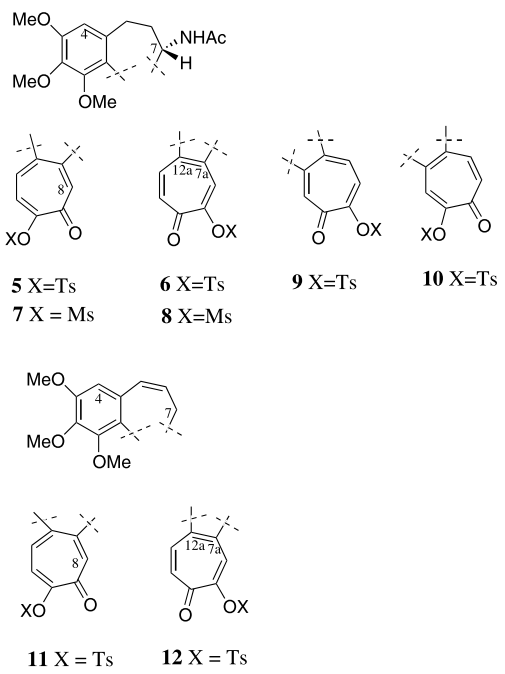

Chart 2.

These processes can be mechanistically described as a shift of the tosyl or mesyl group via intramolecular nucleophilic attack at the sulfur atom by the cycloheptatrienone carbonyl oxygen. To this concern, although the mechanism of nucleophilic substitution at the sulfonyl sulfur atom has been actively investigated, a clear cut position in favor of either a two-step process (with a trigonal bipyramidal intermediate having negatively-charged oxygen atoms at the apical positions) or a one-step process (with entering and leaving group at the apical position of a trigonal bipyramidal transition state) was never taken.[9] The latter configuration is difficult to conceive for the reactions described here, because collinear entering and leaving tropolonate-like oxygen atoms would give rise to a prohibitively highly strained transition state. Rather, a trigonal bipyramidal intermediate having negatively-charged oxygen atoms at the apical positions, as outlined above, can be easily accommodated for the reactions described here: molecular mechanics calculations by the MMFF94 force field for the hypothetical bipyramidal intermediate for fluxional system **2a**/**2b** (1) indicate low strain. Higher rates in DMF than toluene for the **3**/**4** equilibrium system (Table 1) are consistent with the highly polarized character of the rate limiting transition state that can be envisaged from the intermediate in Figure 1.

These tosyl migrations may allow recycling biologically-inactive isocolchicinoids into biologically-active colchicinoids. This affords synthetic value to the unselective tosylation or mesylation of colchiceine, which remains the easiest intermediate step towards a variety of colchicinoids.[4,6]

Table 1. Rate coefficients for the equilibriation reactions in DMF

Equilibrating compounds	k_1 (s^{-1} 10^5)[a]			k_{-1} (s^{-1} 10^5)[a]		
	100°C	118°C	140°C	100°C	118°C	140°C
3/**4**	3.4±0.1	19.7	89	3.9±0.1	22.7	107
3/**4**		16.0[b]			18.0[b]	
5/**6**	5.8±0.1	30.0	172	2.3±0.1	13.0	72
7/**8**	6.5±0.1	36.5	214	3.3±0.1	17.7	107
9/**10**	5.2±0.1	27.7	150	1.9±0.1	10.2	60
11/**12**	3.5±0.1	28.9	87	1.4±0.1	8.4	36

[a] k_1 and k_{-1} represent first-order rate coefficients for the direct (e.g. **3**→**4**) and the reverse (e.g. **4**→**3**) reactions.
[b] Measured in toluene.

Table 2. Activation parameters for the equilibration reactions in DMF

Equilibrating compounds	$\Delta H^{\neq}_{25°}$ (kcal/mol)[a]	$\Delta S^{\neq}_{25°}$ (e.u.)[a]	$\Delta H^{\neq}_{25°}$ (kcal/mol)[b]	$\Delta S^{\neq}_{25°}$ (e.u.)[b]
3/**4**	24.3	−14.1	24.7	−12.8
5/**6**	25.3	−10.4	25.7	−11.2
7/**8**	26.1	−8.1	26.0	−9.7
9/**10**	25.1	−11.2	25.8	−11.4
11/**12**	23.8	−15.2	23.8	−16.9

[a] Activation parameters for the direct reaction.
[b] Activation parameters for the reverse reaction.

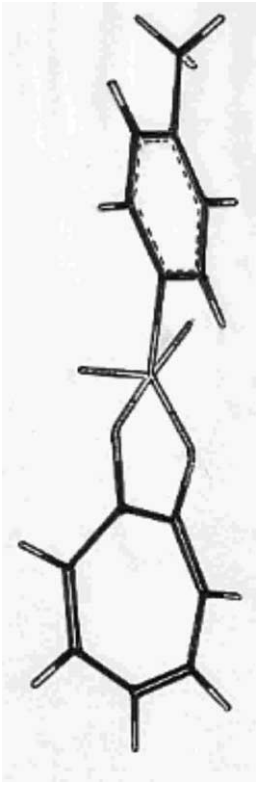

Figure 1. MMFF94-calculated least-strained hypothetical bipyramidal intermediate for the intramolecular shift of the tosyl group with tropolone tosylate.

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3. Prepared according to Sato, T. *Nippon Kagaku Zasshi* **1956**, *80*, 1056. On TLC separation two isomeric tosylates were obtained. The ^{1}H NMR spectrum of the isomer characterized by a lower m.p. (79–81°C) supports the structure previously assigned to **3**. 2-Tosyloxy-4-isopropyltropone (**3**): δ_H (C_6D_6) 8.12 (d, J=8.4), 7.42 (d, J(3,5)=1.6, H3), 6.80 (d, J(7,6)=12.2, H7), 6.68 (d, J=8.4), 6.17 (dd, J(6,7)=12.2, J(6,5)=9.7, H6), 6.00 (dd, J(5,6)=9.7, J(5,3)=1.6, H5), 2.05 (heptet, J=6.6, isopropyl methyne), 1.74 (s, tosyl methyl), 0.74 (d, J=6.6, isopropyl methyl groups). Therefore, the isomer with higher m.p. could be assigned structure **4**.
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7. Compounds **11** and **12** were prepared by tosylation of 5,6-didehydro-7-deacetamidocolchiceine (Kouroupis, P.; Hansen, H.-J. *Helv. Chim. Acta* **1995**, *78*, 1247-1277). The reaction mixture was subjected to TLC on silica gel with Et_2O. The R_f 0.57 band gave **12** while the R_f 0.61 band gave **11**. Compound **11**: δ_H ($CDCl_3$) 7.96 (d, J=8.4), 7.38 (d, J(12,11)=10.2, H12), 7.37 (d, J =8.4), 7.21 (s, H8), 7.05 (d, J(11,12)=10.2, H11), 6.56 (s, H4), 6.54 (dd, J(5,6)=10.1, J(5,7$_{ax}$)=1.4, H5), 6.20 (m, H6), 3.96, 3.93 and 3.65 (three s, OMe), 3.05 (m, H7$_{eq}$ and H7$_{ax}$), 2.48 (s, tosyl methyl), δ_C ($CDCl_3$): 181, 154.4, 145.2, 137.4, 133.9, 129.9, 129.7, 128.7, 107.0, 61.7, 56.4, 39.3, 22.3. Compound **12**: δ_H ($CDCl_3$) 7.96 (d, J=8.5), 7.58 (s, H8), 7.38 (d, J(12,11)=13.2, H12), 6.91 (d, J(11,12)=13.2, H11), 6.66 (s, H4), 6.59 (dd, J(5,6)=9.6, J(5,7$_{ax}$)=1.4, H5), 6.23 (ddd, J(6,5)=9.6, J(6,7$_{eq}$) =12.4, J(6,7$_{ax}$)=1.8, H6), 3.95, 3.93 and 3.74 (three s, OMe), 3.07 (dd, J(7$_{eq}$,6)=12.4, J(7$_{eq}$,7$_{ax}$)=6.0, H7$_{eq}$), 2.52 (dd, J(7$_{ax}$,7$_{eq}$)=6.0, J(7$_{ax}$,6)=1.8, H7$_{ax}$), 2.45 (s, tosyl methyl), δ_C($CDCl_3$): 178.5, 153.7, 152.2, 145.6, 142.7, 141.4, 138.9, 135.4, 133.8, 133.6, 130.9, 129.8, 128.9, 106.7, 61.6, 56.3, 37.5, 22.1.
8. Kinetics measurements were carried out with about 10^{-3} mol L^{-1} solutions in dry DMF. The solutions, sealed in vials, were heated in a thermostatic bath and were analysed by HPLC under UV detection. For the **5**/**6** system a RP-18 250 mm column, with MeCN/H_2O 6:4, flow rate 1 mL/min, gave retention times 4.8 min for **6** and 5.2 min for **5**. For both systems **7**/**8** and **9**/**10** a CN 250 mm column, eluent AcOEt, flow rate 1 mL/min, gave retention times 3.12 min for **8**, 3.4 min for **7**, 3.5 min for **9** and 4.0 min for **10**. A CN 250 mm column with AcOEt/hexane 6:4, flow rate 1 mL/min, gave retention times 3.36 min for **4**, 4.03 min for **3**, 3.56 min for **12** and 4.11 for **11**.
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