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Tautomeric selectivity towards colchicinoids in the tosylation of colchiceine on a heterogeneous, easily removable catalyst

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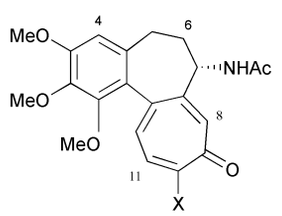
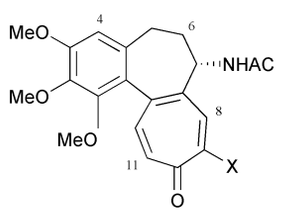
Here is presented an easy, rapid new method of tosylation of compounds containing acidic OH groups, such as tropolones and phenols, on a solid, removable catalyst, Amberlite IRA-400(OH); of special value is the preferential selectivity for the colchiceine tautomer 1a, leading to 10-tosyloxycolchicide (2)—the precursor of a variety of bioactive colchicinoids—which inverts the result of previous tosylation methodologies leading preferentially to useless 9-tosyloxyisocolchicide (3).

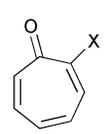
Tosylation of colchiceine (**1a/1b**) by equimolar tosyl chloride (TsCl) in a large-excess of pyridine at room temperature for 24 h [1a] has become standard technology towards a wide variety of colchicine derivatives, resulting from the nucleophilic replacement of the 10-tosyloxy group of 10-tosyloxycolchicide (**2**). Nucleophiles include azido,[1a] halo,[1b] amino,[1c] alkoxy,[1d,e] and alkyl- and phenylthio groups.[1f] With nucleophiles carrying a second reactive functionality, condensation with the cycloheptatrienone carbonyl group may ensue, affording 1,3-diazaazulene [1e] and fused furano derivatives.[2]



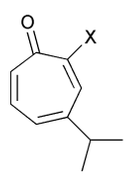
1a X = OH
2 X = OTs
4 X = OMs



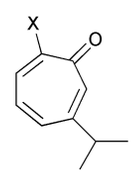
1b X = OH
3 X = OTs
5 X = OMs



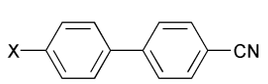
6 X = OH
7 X = OTs



8a X = OH
9 X = OTs



8b X = OH
10 X = OTs



11 X = OH
12 X = OTs

However, because of the vinylogous acid nature of colchiceine, which means that **1a** and **1b** are in tautomeric equilibrium under the tosylation conditions, this results in a mixture of 74.0% 9-tosyloxyisocolchicide (**3**) and 26.0% 10-tosyloxycolchicide (**2**), according to our HPLC analysis (Table 1). Although the overall yield is good (*ca.* 90%), **2** can be obtained in only 22% isolated yield.[1a] This is vexing because it is just this isomer that may give access to antimitotic, albeit toxic, colchicine,[3a,4] or, in transformation procedures, to less toxic [3b] colchicine derivatives endowed with stronger antitumor activity,[3b] while all known isocolchicine derivatives (prepared from isomer **3**) have proven to be biologically inactive.[3a] The slowness of tosylation in pyridine,[1a] which is a noxious chemical, and the somewhat difficult recovery of tosylates from the reaction mixture, constitute additional drawbacks. Clearly, an improved technology toward 10-tosyloxycolchicide (**2**) is desirable.

We provide here preliminary indications as to a new methodology of tosylation of colchiceine, affording 10-tosyloxycolchicide (**2**) more rapidly and cleanly, in higher yield, and with simpler recovery than in the above described "pyridine technology".[1a] From the latter we progressed as follows. On replacing $CHCl_3$ with CH_2Cl_2 in Kabalka's general tosylation methodology (substrate–TsCl–pyridine in molar ratio 1 : 1.5 : 2 in $CHCl_3$),[5] the HPLC-evaluated percentage of 10-tosyloxycolchicide (**2**) in the **2/3** mixture, was raised to 38.4% (Table 1). By further replacement of pyridine [6a] with, in turn, brucine,[6b] 1,4-diazabicyclo[2.2.2]octane (DABCO),[6c] triethylamine,[6c] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[6a] and *N,N,N′,N′*-tetramethyl-1,8-naphthalenediamine (proton-sponge),[6a] the percentage of **2** became 38.5, 35.5, 49.5, 52.6, and 59.0%, respectively (Table 1). Finally, the best percentage of **2** (70.5%) was obtained under heterogeneous catalysis by dry Amberlite IRA-400 (OH), a strongly basic gel-type resin, in CH_2Cl_2 at −10 °C (Table 1). †

Replacing TsCl with mesyl chloride, mesylation of colchiceine was obtained. The best relative percentage of the desired 10-mesyloxycolchicide (**4**)[7] (52.9%) was obtained with proton-sponge. Amberlite IRA-400(OH), triethylamine, and pyridine gave **4** in 41.0, 33.1, and 25.0% relative percentages.

This Amberlite IRA-400(OH) technology applies also to other vinylogous carboxylic acids, like tropolone (**6**) and β-thujaplicin (**8a/8b**), affording tosylates **7** and **9/10**, respectively, although in the latter case the relative percentage of isomer **10** was increased by a mere 2.4% with respect to a 1 : 1 ratio from the "pyridine technology".[7] Even phenolic compounds, like 4′-hydroxy-4-biphenylcarbonitrile **11**, are tosylated using Amberlite IRA-400(OH), like in the montmorillonite clay technology.[8] In our hands, **11** gave **12**[9] in nearly quantitative yield. †

Although comparing solution conditions with heterogeneous catalysis in the liquid phase, and dealing with basicity in non-aqueous media is difficult, it should be noticed that progress towards better yields of the desired 10-tosyloxycolchicide (**2**) runs roughly in parallel to increasing basicity of the catalyst used (Table 1).[6a,b,c,10] This behaviour may be accounted for by a balance between acidity [11] and nucleophilicity [12] of **1a** and **1b**, which must be a delicate affair, since the trend was disrupted for mesylation, as shown above. Notably, this study has revealed

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Table 1 Ionization constants (pK_a) of BH^+ in H_2O and HPLC-evaluated percentages of **2/3** (isolated yields) on tosylation of colchiceine (**1a/1b**)

Base (B)-medium	pK_a	**2**	**3**
Pyridine (neat)	5.2[6a]	26.0 (22)	74.0 (67)
Pyridine-CH_2Cl_2	5.2[6a]	38.4	61.6
Brucine-CH_2Cl_2	8.28[6b]	38.5	61.5
DABCO-CH_2Cl_2	8.7[6c]	35.5	64.5
Triethylamine-CH_2Cl_2	10.68[6c]	49.5	50.5
DBU-CH_2Cl_2	12[6a]	52.6	47.4
Proton-sponge-CH_2Cl_2	12.1[6a]	59.0	41.0
Amberlite IRA-400 (OH)–CH_2Cl_2 rt		67.0 (60)	33.0 (30)
Amberlite IRA-400 (OH)–CH_2Cl_2 −10 °C		70.4 (63)	29.5 (26)

the first case of tautomeric selectivity in vinylogous acyl sulfonate preparation from vinylogous carboxylic acids. Full light on the range of applicability of this new methodology, and the factors involved, must await further experimentation.

Notes and references

† *General procedure.* Amberlite IRA-400(OH), Aldrich, 10 g was stepwise washed on a sintered glass funnel with H_2O, 5% NaOH (100 mL each), H_2O until neutrality, EtOH and Et_2O (50 mL each), and then dried *in vacuo* on P_4O_{10} and stored under N_2.

To 0.26 mmol of substrate in 5 mL CH_2Cl_2 were added 0.55 g of dry Amberlite IRA-400 under N_2, followed by TsCl, (0.076 g, 0.40 mmol) or MsCl (0.046 g, 0.40 mmol) under stirring. HPLC monitoring showed completion of the process in *ca.* 20 min at rt. The slurry was filtered, then the solvent was removed *in vacuo*. With **1a/1b** and **8a/8b** the residue was subjected to TLC for the separation of the isomeric products, whereas with **6** and **11** the residue was simply purified by recrystallization. For the tosylation of **1a/1b**, HPLC monitoring of the reaction mixture revealed 67.0% **2** and 33.0% **3** (Table 1). After silica-gel G F Analtech TLC with $CHCl_3$–$(CH_3)_2CO$ 3 : 2, **2** and **3** were isolated from the $R_f = 0.62$ and 0.76 bands in 60 and 30% yields, respectively. Carrying out the tosylation of **1a/1b** at −10 °C, the HPLC-evaluated percentage of **2** rose to 70.5%, although the process was slowed down by one order of magnitude with respect to rt conditions. TLC separation as above gave **2** and **3** in 63 and 26% yields respectively (Table 1). On further lowering the temperature, the tosylation process became impracticably slow. No equilibration of tosylates[7] was observed during these processes.

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4 The last step of several classical colchicine total syntheses (see, for example, J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall and A. Eschenmoser, *Helv. Chim. Acta*, 1961, **44**, 540; J. Martel, E. Toromanoff and C. Huynh, *J. Org. Chem.*, 1965, **30**, 1752; D. L. Boger and C. E. Brotherton, *J. Am. Chem. Soc.*, 1986, **108**, 6713) consists of alkylation of colchiceine, which, in current methodologies, such as diazomethane treatment (M. Sorkin, *Helv. Chim. Acta*, 1946, **29**, 246) suffers from preferential isocolchicine formation (55 : 45). The Amberlite route provided here may considerably enhance the yield of the process.

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9 N. Ayako, M. Ayako, W. Takeo, I. Osami, *Jpn. Kokai Tokkyo Koho JP* 06,247,911/1994, CAN 122 : 252233x; . Data for **12**: Mp 102 °C; IR (Nujol) *ν* 2223, 1607, 1596, 1369, 1197, 1179, 1154, 874, 863, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) *δ* 2.47 (s, 3H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) *δ* 21.8, 111.3, 118.7, 123.0, 127.6, 128.4, 129.8, 132.6, 138.0, 144.1, 145.6, 149.8. Anal. Calcd for $C_{20}H_{15}NO_3S$: C, 68.77; H, 4.30; N 4.01; Found: C, 68.49; H 4.20; N 3.95%.

10 In this respect, the pK_a for brucine and DABCO are too close together for the observed yield inversion (Table 1) to be significant.

11 Calculations by the Advanced Chemistry Development (ACD) Software Solaris V4.67 gave pK_a values 7.70 and 7.24 for **1a** and **1b**, respectively.

12 Nucleophilic substitutions on colchicides and isocolchicides bearing an α-leaving group were previously compared: M. Cavazza and F. Pietra, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2657.