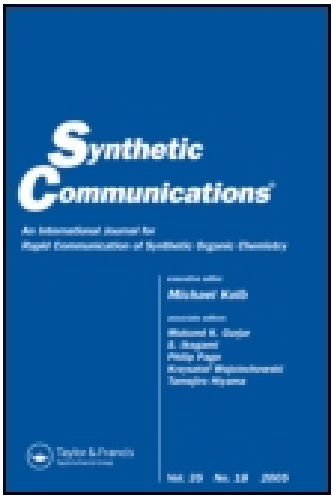

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A General Entry to 10-Halocolchicides and 9-Haloisocolchicides

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A GENERAL ENTRY TO 10-HALOCOLCHICIDES AND 9-HALOISOCOLCHICIDES

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Abstract: Readily accessible 10-tosyloxycolchicide (**1**) and LiX (X=Cl or Br or I) in $MeOH/BF_3{\cdot}Et_2O$ at reflux give 10-chloro- (**2**), 10-bromo- (**4**), or 10-iodocolchicide (**5**), in good yields. 9-Chloro- (**7**) and 9-bromoisocolchidide (**8**) can be similarly obtained from 9-tosyloxyisocolchidide (**6**) and the method applies also to troponoids.

From early therapeutic applications,[1] colchicinoids have remained in use as laboratory tools for cancer studies.[2] There is also a renewed interest by the industry towards colchicinoids as bioactive compounds for the control of pests. Moreover, interest continues in troponoids as intermediates for the synthesis of compounds in a variety of classes[3] or as an endless mine for theoretical advances in organic chemistry.[4]

All these activities may require, as intermediates,[5] functionalised troponoids and, to the extent that analogy holds,[6] also functionalised colchicinoids. We have recently

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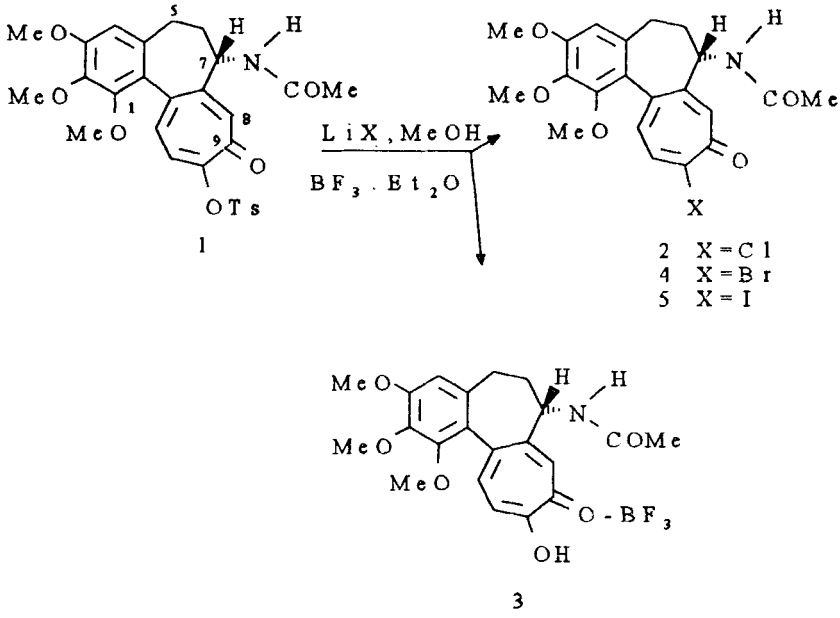
offered some solutions to these problems[7] but the need remains of haloderivatives as key intermediates towards a variety of substituted troponoids[5] and colchicinoids.

Scheme 1



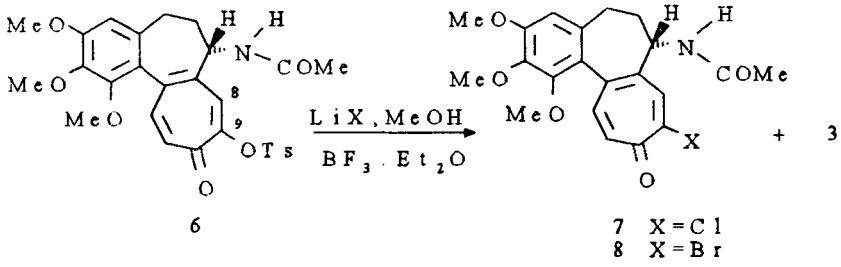
1 3

Actually, different technologies are required for different halotroponoids and yields are in any case poor.[8] As to the colchicinoids, only 10-fluorocolchicide and 9-fluoroisocolchicide (from colchiceine and SF_4)[7c] and 10-chlorocolchicide and 9-chloroisocolchicide (from the treatment of colchiceine with $SOCl_2$) have been described.[7c] Except for 10-fluorocolchicide yields of the above reactions were quite poor,[7c] while technologies for bromo- and iodotropones[8] are destructive of the colchicinoid skeleton.

We offer here an alternative, simple methodology of access to new halocolchicinoids and haloisocolchicinoids from easily available tosylates of colchiceine,[9] which also allows smoother access than current methodologies to known halocolchicinoids and troponoids.

In a typical procedure a solution of 10-tosyloxycolchicide[9] (**1**, Scheme 1) and a

Scheme 2



6

7 X = Cl
8 X = Br

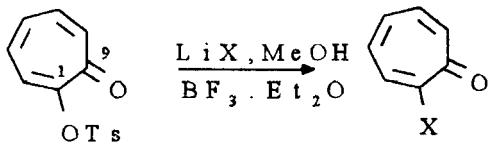
tenfold excess of $BF_3{\cdot}Et_2O$ in the presence of 5 M LiCl were briefly heated at reflux in MeOH, evaporated, extracted, and the mixture was separated into 10-chlorocolchicide[7c] (**2**) (70%) and the colchiceine-BF_3 adduct **3**[7b] (15%). We obtained similarly 10-bromocolchicide (**4**) (43%) and 10-iodocolchicide (**5**) (50%) accompanied by **3** (46% in either case). The use of $BF_3{\cdot}Et_2O$ in excess was only dictated by practical reasons of a dosage in small scale reactions; selected experiments with **1** showed that a slight excess of $BF_3{\cdot}Et_2O$ gives equally satisfactory results.

The synthesis of haloisocolchicides was carried out analogously, except for longer

reflux times, from 9-tosyloxyisocolchicide (**6**) obtaining 9-chloroisocolchicide (**7**)[7c] (63%) and 9-bromoisocolchicide (**8**) (34%) accompanied by **3** (32 and 52%, respectively) (Scheme 2). When **6** was treated with LiI, under otherwise the conditions used for **7** and **8**, **3** could be isolated as the sole product in 60% yield. This is the only limitation we have met for these reactions.

This methodology was extended to the halotropones (Scheme 2), where reflux times even longer than for the synthesis of haloisocolchicides were required, obtaining **10**, **11**, or **12** in 60, 32, and 30% yields, respectively. No tropolone BF_3 adduct[7c] was detected among the products.

Scheme 3



9

10 X = Cl
11 X = Br
12 X = I

In summary, $BF_3{\cdot}Et_2O$ proved to be an efficient catalyst for the activation of the troponoid system to nucleophilic substitution, remedying, for the sensitive colchicinoids, to the ravaging effects of strong proton acids in use for troponoids.[8] An additional advantage of $BF_3{\cdot}Et_2O$ is that the by-product, colchicide, is trapped as a form (**3**) that allows easy entry into aminocolchicinoids.[7b]

EXPERIMENTAL SECTION

All evaporations were carried out at reduced pressure. Preparative TLC was carried out on 2 mm thick Merck Si60 PF_{254} plates, eluent 1:1 acetone-$CHCl_3$. HPLC was performed with 8 x 250 mm RP18 column with 1:1 CH_3CN-H_2O, flux 3 mL min^{-1}, UV monitoring at λ = 260 nm. NMR spectra were recorded in $CDCl_3$ solution at 200 MHz on a Varian Gemini BB spectrometer; chemical shifts are expressed in δ, ppm, with respect to internal Me_4Si (= 0 ppm) and *J* values in Hz. Mass spectra (EI) were taken with a Kratos-MS80 mass spectrometer with home-built computerized system. UV spectra were recorded with a Perkin-Elmer Hitachi200 spectrophotometer.

10-Chlorocolchicide (2). To 10-tosyloxycolchicide[9] (**1**, Scheme 1) (0.039 g , 7.2 x 10^{-5} mol) in 2 mL of MeOH were added LiCl (0.45 g, 1.1 x 10^{-2} mol) and $BF_3{\cdot}Et_2O$(0.1 mL). The mixture was heated at reflux for 30 min, evaporated to dryness, added of water, and finally $CHCl_3$ extracted. The organic extract was dried over Na_2SO_4, evaporated, and the residue was subjected to TLC obtaining 10-chlorocolchicide (**2**)[7c] (R_F = 0.50, 0.020 g, 5.1 x 10^{-5} mol, 70%) and adduct **3**[7b] (R_F = 0.70, 0.0049 g, 1.1 x 10^{-5} mol, 15%). Similar yields were obtained using only 0.015 mL of $BF_3{\cdot}Et_2O$ under otherwise identical conditions.

10-Bromocolchicide (4). To 10-tosyloxycolchicide[9] (**1**, Scheme 1) (0.039 g , 7.2 x 10^{-5} mol) in 2 mL of MeOH were added LiBr (0.59 g, 6.8 x 10^{-3} mol) and $BF_3{\cdot}Et_2O$ (0.1 mL). Proceeding as for **2** above, we obtained 10-bromocolchicide (**4**) (R_F = 0.55, 0.014 g, 3.1 x 10^{-5} mol, 43%) and adduct **3**[7b] (R_F = 0.70, 0.015 g, 3.3 x 10^{-5} mol,

46%). Data of **4**: UV (MeOH), λ_{max} (logϵ) 375 (3.6), 248 (3.9). ^{1}H NMR ($CDCl_3$) δ_H 2.00 (s, $COCH_3$), 2.15-2.35 (series of m, H_2-C6), 2.55 (m, H_2-C5), 3.68, 3.90, 3.94 (3s, 3 MeO), 4.60 (td, J = 12.6, 7.32, H-C7), 6.37 (d, J = 7.32, NH), 6.53 (s, H-C4), 7.06 (d, J = 10.4, H-C12), 7.40 (s, H-C8), 8.05 (d, J = 10.4, H-C11). ^{13}C NMR ($CDCl_3$) 180.42, 169.88, 154.20, 151.25, 141.79, 140.95, 134.16, 133.42, 128.38, 124.90, 107.50, 60.60, 60.50, 56.1, 29.76, 28.96, 23.1. MS-EI *m/z* (%) 447/449 (96/100, $M^{+\cdot}$), 419/421 (69/74, $[M - CO]^{+\cdot}$), 368 (51, $[M - Br]^+$). HR-MS-EI *m/z* 447 447.06854±0.0004. Calc. for $C_{21}H_{22}Br_{79}NO_5$ 447.06812.

10-Iodolchicide (5). To 10-tosyloxycolchicide[9] (**1**, Scheme 1) (0.039 g , 7.2 x 10^{-5} mol) in 2 mL of MeOH were added LiI (0.61 g, 4.6 x 10^{-3} mol) and $BF_3{\cdot}Et_2O$ (0.1 mL). Proceeding as for **2** above, we obtained 10-iodocolchicide (**5**) (R_F = 0.58, 0.018 g, 3.6 x 10^{-5} mol, 50%) and adduct **3**[7b] (R_F = 0.70, 0.015 g, 3..3 x 10^{-5} mol, 46%). Data of **5**: UV (MeOH), λ_{max} (logϵ) 480 (3.6), 250sh. δ_H ($CDCl_3$) only data differing from **4** are given 4.62 (m, H-C7), 6.52 (s, H-C4), 6.89 (d, J = 10.2, H-C12), 7.38 (s, H-C8), 8.45 (d, J = 10.2, H-C11). δ_C 178.20, 165.81, 150.0, 147.20, 141.20, 137.55, 130.49, 130.05, 125.64, 124.80, 124.29, 120.76, 103.33, 57.68, 57.37. MS-EI *m/z* (%) 495 (55, $M^{+\cdot}$), 467 (46, $[M - CO]^{+\cdot}$), 368 (100, $[M - I]^+$). HR-MS-EI *m/z* 495 495.005230±0.002 (a superimposed small signal for an impurity is responsible for the lower precision in this case). Calc. for $C_{21}H_{22}INO_5$ 495.05426.

9-Chloroisocolchicide (7). To 9-tosyloxyisocolchicide[9] (**6**, Scheme 2) (0.035 g, 6.5 x 10^{-5} mol) in 2 mL of MeOH were added LiCl (0.409 g, 9.6 x 10^{-3}mol) and

$BF_3{\cdot}Et_2O$ (0.1 mL). Proceeding as for **2**, except for 60 min of reflux, we obtained 9-chloroisocolchicide (**7**) (R_F = 0.66, 0.016 g, 4.1 x 10^{-5} mol, 66%) and adduct **3**[7b] (R_F = 0.70, 0.009 g, 2.0 x 10^{-5} mol, 31%).

9-Bromoisocolchicide (8). To 9-tosyloxyisocolchicide[9] (**6**, Scheme 2) (0.035 g, 6.5 x 10^{-5} mol) in 2 mL of MeOH were added LiBr (0.670 g, 7.7 x 10^{-3} mol) and $BF_3{\cdot}Et_2O$ (0.1 mL). Proceeding as for **7** above, except for separating the products by HPLC, we obtained 9-bromoisocolchicide (**8**) (t_R = 5.9 min, 0.010 g, 2.2 x 10^{-5} mol, 34%) and adduct **3**[7b], (t_R = 8.1 min, 0.015 g, 3.3 x 10^{-5} mol, 51%). Data of **8**: UV (MeOH), λ_{max} (logϵ) 370 (3.7), 248 (4.0). δ_H 2.06 (s, $COCH_3$), 2.15-2.35 (series of m, H_2-C6), 2.55 (m, H_2-C5), 3.70, 3.91, 3.93 (3s, MeO's), 4.55 (td, *J* = 12.6, 5.85, H-C7), 5.94 (d, *J* = 5.85, NH), 6.57 (s, H-C4), 7.12 (d, *J* = 13.0, H-C12), 7.37 (d, *J* = 13.0, H-C11), 8.19 (s, H-C8). MS-EI *m/z* (%) 447/449 (69/70, $M^{+\cdot}$), 419/421 (92/100, $[M - CO]^{+\cdot}$), 368 (48, $[M - Br]^+$). HR-MS-EI *m/z* 447 447.06789±0.0002. Calc. for $C_{21}H_{22}Br_{79}NO_5$ 447.06812.

Reaction of 9-tosyloxyisocolchicide (6) with LiI. To 9-tosyloxyisocolchicide[9] (**6**, Scheme 2) (0.035 g , 6.5 x 10^{-5} mol) in 2 mL of MeOH were added LiI (0.612 g, 4.6 x 10^{-3} mol) and $BF_3{\cdot}Et_2O$ (0.1 mL). Proceeding as for **7** above we obtained adduct **3**[7b], (0.018 g, 3.9 x 10^{-5} mol, 61%) as the sole isolable product.

2-Chlorotropone (10). To 2-tosyloxytropone[10] (**9**, Scheme 3) (0.047 g , 1.7 x 10^{-4} mol) in 2 mL of MeOH were added LiCl (0.45 g, 1.1 x 10^{-2} mol) and $BF_3{\cdot}Et_2O$ (0.1

mL). This mixture was heated at reflux for 60 min, evaporated to dryness, added of water, and finally $CHCl_3$ extracted. The organic extract was dried over Na_2SO_4, evaporated, and the residue subjected to TLC to give 2-chlorotropone (**10**)[10] (0.014 g, 1.02×10^{-4} mol, 60%).

2-Bromotropone (11). To 2-tosyloxytropone[10] (**9**, Scheme 3) (0.047 g , 1.7×10^{-4} mol) in 2 mL of MeOH were added LiBr (0.61 g, 7.0×10^{-3} mol) and $BF_3{\cdot}Et_2O$ (0.1 mL). This mixture was heated at reflux for 1.5 h, evaporated to dryness, added of water, and finally $CHCl_3$ extracted. The organic extract was dried over Na_2SO_4, evaporated, and the residue subjected to TLC to give 2-bromotropone (**11**)[8] (0.010 g, 5.46×10^{-5} mol, 32%).

2-Iodotropone (12). To 2-tosyloxytropone[10] (**9**, Scheme 3) (0.047 g , 1.7×10^{-4} mol) in 2 mL of MeOH were added LiI (0.66 g, 5.0×10^{-3} mol) and $BF_3{\cdot}Et_2O$ (0.1 mL). This mixture was heated at reflux for 5 h and then worked up as for **11** obtaining 2-iodotropone (**12**)[8] (0.012 g, 5.2×10^{-5} mol, 30%).

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