Re-functionalization of 9-Substituted Isocolchicides via Nucleophilic Tele-Substitution. A General Synthesis of 11-Alkyl(Aryl)thioisocolchicides

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9-Substituted isocolchicides in methanol or dimethyl sulfoxide undergo ipso-substitution by sodium thiocyanate to give 11-alkyl(aryl)thio-substituted isocolchicides which are prone to in situ tele-substitution affording 11-alkyl(aryl)thio-functionalized isocolchicides. Such C-11 activation by dicoordinated sulfur is used here for a general synthesis of 11-alkyl(aryl)thioisocolchicides.

Introduction

Despite keen interest in colchicine and its derivatives (colchicinoids) by chemists, biologists and pharmacologists, very little is known about the 11-substituted isocolchicide series. Until recently, only two members of this series were known, i.e. 11-methylthio- \cite{1,2} and 11-amino-isocolchicide \cite{3}. The way they are formed is interesting: re-examination of Velluz’s reaction of isocolchicine with sodium methanethiolate to give 11-methylthioisocolchicide \cite{1,2} led us to establish that this compound is formed via initial ipso replacement of the methoxy group of isocolchicine by the thiolate to give 9-methylthioisocolchicide (1); the latter undergoes tele-substitution at C-11 by the thiolate \cite{4}. This is in keeping with general rules concerning electron acceptance by dicoordinated sulfur at C-9 in simple troponoids \cite{5}. On this basis, we recently succeeded in the C-11 refunctionalization of 9-substituted isocolchicides by primary or secondary amines: isocolchicides carrying a C-9 activating nucleofugic group like SCH\textsubscript{3}, SO\textsubscript{2}CH\textsubscript{3} or Cl were found to undergo tele-substitution at C-11 by the amine in dimethyl sulfoxide in competition with ipso-substitution at C-9 \cite{6}. Thus, on treating 1 in dimethyl sulfoxide at 64°C with excess amine, ca. 1:1 mixtures of 9- and 11-amino substituted isocolchicides were obtained, including 11-piperidino \cite{6}, -11-morpholino \cite{7} and 11-n-propylaminoisocolchicide \cite{7}. Here we present an extension of the above methodology leading to a general synthesis of 11-alkyl(aryl)thioisocolchicides.

Results and Discussion

Treatment of 1 or 9-tosylisocolchicide (2) with methanol containing ca. 35 mol. equiv. of \textit{in situ} prepared sodium thiolate, led to mixtures of 9-substituted and 11-substituted isocolchicides that were collected and separated by Thin-Layer Chromatography after that the reaction mixtures were left for 20 h at room temperature (Scheme 1 and Table I). Similar results were obtained by addition of ca. 35 mol. equiv. of sodium thiolate and 1.2 mol. equiv. of thiol to solutions of 1 or 2 in dimethyl sulfoxide (Scheme1). Comparison of these thiolate reactions with those of the same substrates with amines reveals interesting differences. Thus, while for the amine reactions it is necessary to start with a substrate that, like 1, carries an activating (i.e. tele-directing) C-9 substituent, there is no such a need for the thiolate reactions: the more easily accessible tosylate 2 \cite{8} proved to be quite convenient, undergoing fast irreversible ipso-substitution by the thiolate to give corresponding 9-alkyl(aryl)thioisocolchicide that takes part to equilibria leading to the tele-substitution product (Scheme 2). However, unlike in reactions with pri-

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Scheme 1.

Table I. Product-yield in the preparative reactions carried out with 1 or 2 and excess thiolate in MeOH at room temperature.
mary or secondary amines, which act both as nucleophiles and protonating agents [9] in reactions with thiolates in aprotic dimethyl sulfoxide an extra source of protons is needed: a slight excess of free thiol was added to establish the protonation equilibria (Scheme 2). In the absence of free thiol, only ipso-substitution was observed. Although in some cases, e.g. with sodium iso-propionate and a home-built computerized acquisition system. Melting points were obtained with Reichert Thermovar apparatus and are uncorrected.

Experimental

General

1H NMR and 13C NMR spectra were obtained with a Gemini Varian BB spectrometer 200 MHz, in CDCl3 as the solvent, unless otherwise stated, TMS as an internal standard. Mass spectra (El) were taken with a Kratos MS80 spectrometer with a Gemini Varian BB spectrometer 200 MHz, and UV A max(MeOH)/nm: 267, 300, 420sh. MS m/z: 457 (15, M%), 398 (21). HRMS m/z obs: 475.19177 (M+), calc. for C25H30O4NS: 457.19229.

(S)-N-(5,6,7,10-Tetrahydro-1,2,3-trimethoxy-9-butythio-10-oxobenzo[ajheptalen-7-yl]acetamide (3)

Yellow solid, Rf=0.47, m.p. 221–223°C dec.
1H NMR: δ= 0.93 (3H, t, J=7.2, CH3C,H3), 1.50 (2H, m, CH3CH2C2H5), 1.73 (2H, m, C2H5CH2CH2), 2.05 (3H, s, Ac), 2.55–2.2 (4H, series of m, 6-H and 5-H), 2.87 (2H, m, SCH2C2H5), 3.92, 3.89, 3.66 (3 x 3H, s, for the 3 MeO), 4.60 (1H, td, J=12.5, 6.3, 7-H), 5.65 (1H, s, 4-H), 7.41 and 6.97 [2H, AB system, J(AB)=12.5, 11-H and 12-H], 7.40 (1H, s, 8-H).
13C NMR: δ=182.33, 169.83, 157.08, 153.78, 143.55, 141.10, 136.63, 134.82, 131.43, 125.89, 124.47, 107.43, 61.60, 61.50, 56.17, 52.95, 38.49, 31.73, 29.94, 29.75, 29.56, 22.95, 22.45, 13.78.

Materials

CH3OH (RS C. Erba) was used as such. DMSO (C. Erba) was distilled from CaH2 under Ar and stored over 3 Å molecular sieves. 9-methylthioisocolchicide 1 [4] and 9-tosyloxyisocolchicide 2 [8] were prepared according to known procedures.

General Procedure

To a stirred solution obtained from Na (0.052g, 2.26 mmol) and dry MeOH (6 ml), were added, under argon, 2.8 mmol of thiol followed by 0.065 mmol of either 1 or 2. The mixture was left for 20 h at room temperature, evaporated under vacuum, and then water was added and the resulting suspension was extracted with CHCl3. The residue from evaporation of the organic phase was subjected to TLC, eluent CHCl3:acetone 3:2, collecting 9-substituted and 11-substituted isocolchicides at the Rf values indicated below and with the yields reported in Table I.

Corresponding reactions were carried out by adding to 0.05 mmol of either 1 or 2 in dried DMSO, under argon, 1.6 mmol of sodium thiolate followed by 0.06 mmol of thiol. These mixtures were worked up as for reactions in MeOH.
181.20, 169.58, 142.88, 140.75, 136.76, 134.72, 132.04, 132.00, 125.11, 107.50, 107.46, 60.08, 56.21, 56.16, 52.94, 38.65, 34.91, 30.09, 29.99, 29.91, 29.75, 23.02, 22.28, 22.09.

UV $\lambda_{\text{max}}$(MeOH)/nm: 260, 290, 363, 386, 402sh.

MS $m/z$ (%): 443 (11, M$^+$), 384 (35).

HRMS $m/z$ obs.: 443.17608 (M$^+$), calc, for C$_{27}$H$_{57}$OSN: 443.17664.

(S)-N-(5,6,7,10-Tetrahydro-1,2,3-trimethoxy-11-i-propylthio-10-oxobenzo[a]heptalen-7-yl)-acetamide (6)

Gummy yellow solid, $R_f=0.42$.

$^1$H NMR $\delta$: 1.42 (6H, d, $J=6.7$, (CH$_3$)$_2$CH), 2.04 (3H, s), 2.60–2.20 (4H, series of m, 6-H and 5-H), 3.33 (1H, heptet, $J=6.7$, Me$_2$CH), 3.94, 3.91, 3.68 (3x3H, s, for the 3 MeO), 4.55 (1H, td, $J=12$, 5.2, 7-H), 5.95 (1H, d, $J=5.2$, NH), 6.58 (1H, s, 4-H), 7.32 and 7.07 [2H, AB system, $J(AB)=12.0$, H-8 and H-9], 7.37 (1H, s, H-12).

UV $\lambda_{\text{max}}$(MeOH)/nm: 267, 332, 402sh.

MS $m/z$ (%): 443 (14, M$^+$), 384 (38).

HRMS $m/z$ obs.: 443.17610 (M$^+$), calc. for C$_{27}$H$_{57}$OSN: 443.17664.

(S)-N-(5,6,7,10-Tetrahydro-1,2,3-trimethoxy-9-(2'-hydroxyethylthio)-10-oxobenzo[a]heptalen-7-yl)-acetamide (7)

Yellow solid, $R_f=0.18$, m.p. 115–117°C.

$^1$H NMR $\delta$: 2.07 (3H, s, Ac), 2.60–2.20 (4H, series of m, 6-H and 5-H), 3.14 (2H, t, SCH$_2$CH$_2$OH), 3.90 (2H, t, HOCH$_2$CH$_2$S), 3.92, 3.90, 3.67 (3x3H, s, for the 3 MeO), 4.61 (1H, m, 7-H), 6.57 (1H, s, 4-H), 7.47 and 6.98 [2H, AB system, $J(AB)=12.5$, H-11 and H-12], 7.66 (1H, s, H-8), 7.95 (1H, br signal, NH).

UV $\lambda_{\text{max}}$(MeOH)/nm: 260, 290, 383, 402sh.

MS $m/z$ (%): 445 (2, M$^+$), 385 (73).

HRMS $m/z$ obs.: 445.15500 (M$^+$), calc. for C$_{27}$H$_{59}$O$_6$N$_5$: 445.15591.

(S)-N-(5,6,7,10-Tetrahydro-1,2,3-trimethoxy-9-phenylthio-10-oxobenzo[a]heptalen-7-yl)-acetamide (9)

Yellow solid, $R_f=0.64$, m.p. 154–155°C.

$^1$H NMR $\delta$: 2.17 (3H, s, Ac), 2.50–2.10 (4H, series of m, 6-H and 5-H), 3.92, 3.87, 3.65 (3x3H, s, for the 3 MeO), 4.41 (1H, td, $J=12.7$, 6.5, 7-H), 5.2 (1H, d, $J=6.7$, NH), 6.52 (1H, s, 4-H), 6.93 (1H, s, 8-H). 7.43 and 7.05 [2H, AB system, $J(AB)=12.5$, 12-H and 11-H], 7.52 (3H, m, phenyl), 7.63 (2H, m, phenyl).

UV $\lambda_{\text{max}}$(MeOH)/nm: 258, 360, 383, 401sh.

MS $m/z$ (%): 477 (14, M$^+$), 449 (17, M-CO), 390 (14).

HRMS $m/z$ obs.: 477.15970 (M$^+$), calc. for C$_{27}$H$_{25}$O$_6$NS: 477.16099.

(S)-N-(5,6,7,10-Tetrahydro-1,2,3-trimethoxy-11-phenylthio-10-oxobenzo[a]heptalen-7-yl)-acetamide (10)

Yellow solid, $R_f=0.35$, m.p. 117–119°C.

$^1$H NMR(CD$_3$COCD$_3$): $\delta$: 1.90 (3H, s, Ac), 2.60–2.10 (4H, series of m, 6-H and 5-H), 3.82, 3.68, 3.52 (3x3H, s, for the 3 MeO), 4.36 (1H, td, $J=12.2$, 6.2, 7-H), 6.67 (1H, s, 4-H), 6.89 (1H, s, 12-H), 7.56 and 7.00 [2H, AB system, $J(AB)=12.6$, 9-H and 8-H], 7.76 (1H, d, $J=6.2$, NH), 7.59–7.45 (5H, m, phenyl).

UV $\lambda_{\text{max}}$(MeOH)/nm: 268, 331, 380, 400sh.

MS $m/z$ (%): 477 (21, M$^+$), 449 (24, M-CO), 390 (19).

HRMS $m/z$ obs.: 477.16043 (M$^+$), calc. for C$_{27}$H$_{25}$O$_6$NS: 477.16099.