Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Selective Demethylation and Demethoxy Thioalkylation of 5-Methoxyindoles

Catherine Caubère [a] , Paul Caubère [a] , Pierre Renard [b] , Jean-Guy Bizot-Espiart [b] & Brigitte Jamart-Grègoire [a]

[a] Laboratoire de Chimmie Organique I , Unité Associée au CNRS, Université de Nancy I , BP 239, F-54506, Vandoeuvre-les-Nancy, France

[b] Adir , 1 Rue Carle Hébert, 92415, Courbevoie, France

Published online: 23 Sep 2006.

To cite this article: Catherine Caubère , Paul Caubère , Pierre Renard , Jean-Guy Bizot-Espiart & Brigitte Jamart-Grègoire (1994) Selective Demethylation and Demethoxy Thioalkylation of 5-Methoxyindoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:13, 1799-1808, DOI: 10.1080/00397919408010187

To link to this article: http://dx.doi.org/10.1080/00397919408010187

SYNTHETIC COMMUNICATIONS, 24(13), 1799-1808 (1994)

SELECTIVE DEMETHYLATION AND DEMETHOXY-THIOALKYLATION OF 5-METHOXYINDOLES

Catherine Caubère[+], Paul Caubère[+], Pierre Renard[‡], Jean-Guy Bizot-Espiart[‡], Brigitte Jamart-Grégoire[*+]

[+]*Laboratoire de Chimie Organique I, Unité Associée au CNRS, Université de Nancy I, BP 239, F-54506 Vandoeuvre-les-Nancy, France*

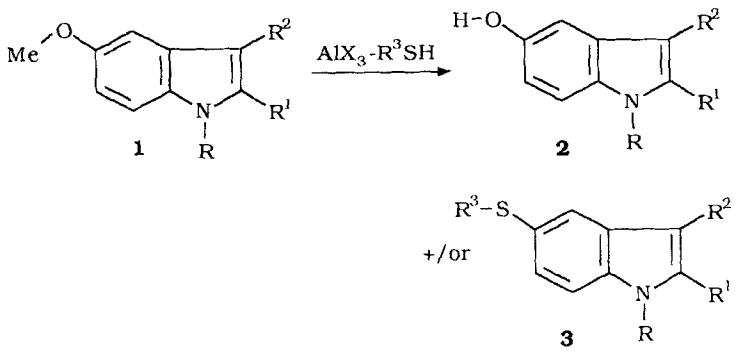
[‡] *Adir, 1 Rue Carle Hébert 92415 Courbevoie, France*

Abstract : Under appropriate conditions, hard acid and soft nucleophile system lead to selective demethylation and demethoxy-thioalkylation of certain 5-methoxyindoles.

During synthesis of 5-hydroxyindoles we were confronted with the necessity to demethylate the corresponding 5-methoxy derivatives. The literature indicates that such reactions can be performed with $AlCl_3$[1] or with the very expensive BBr_3.[2] With our substrates these reagents led to disappointing results.

Curiously, demethylations with aluminium halides associated to thiols[3] have never been investigated in the indoles series.

* To whom correspondence should be addressed.



Scheme 1

In our hands, such reagents led to the unexpected result reported in Scheme 1.

To the best of our knowledge the formation of the thioalkyl products during demethylations with these reagents[3] had never been described before.

In the Table are reported the most significative results of experiments performed with representative substrates and reagents.

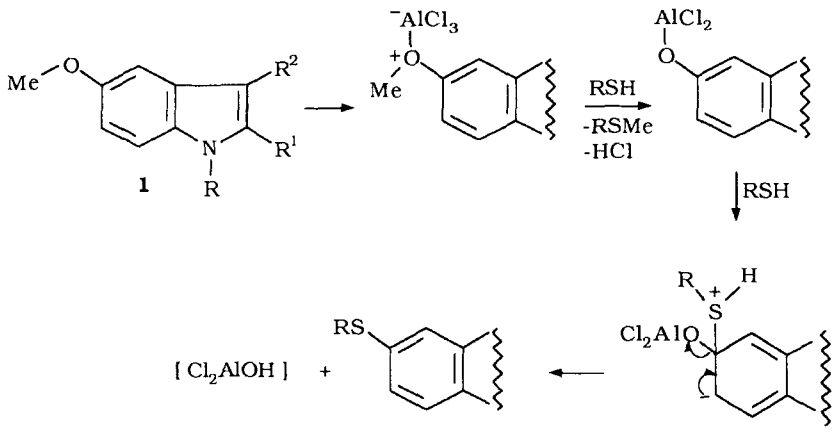
During these study, a number of useful informations emerged.

For a given substrate and thiol $AlBr_3$, which had been found more reactive than $AlCl_3$,[3a] presently appeared as more selective in the formation of **2** but much less efficient in the formation of **3**. On the other hand PhSH, which is of lower nucleophilicity than EtSH, was also less efficient in the formation of **3**. These

Table

Entry	R	R^1	R^2	R^3	X	Conditions [a]	T (°C)	t (h)	**2** % [b]	**3** % [b]
1	Me	$(CH_2)_4$		Et	Br	A	0 →25	17	91	-
2	Me	$(CH_2)_5$		Et	Cl	A	0	3	72	-
3	Me	$(CH_2)_{10}$		Et	Cl	A	0	2.5	68	-
4	Me	CON(Bu)Ph	H	Et	Cl	A	0	2	60	-
5	H	CON(Me)Ph	H	Et	Cl	A	0	3	60	-
6	Me	$(CH_2)_4$		Et	Cl	B	0 →25	48	20	80
7	Me	$(CH_2)_5$		Et	Cl	B	0 →25	147	30	55
8	Me	$(CH_2)_{10}$		Et	Cl	B	0 →25	47	-	80
9	Me	CON(Bu)Ph	H	Et	Cl	B	0 →25	5	43	45
10	H	CON(Me)Ph	H	Et	Cl	B	0	4.5	15	55
11	H	CON(Oct)Ph	H	Et	Cl	B	0	3	30	70
12	H	CON(Oct)Ph	H	Ph	Br	B	0	3	73	-

[a] See experimental part. [b] Isolated yields.



Scheme 2

properties allowed us to perform the selective demethylation of run 1 and 12 which cannot be obtained with the couple $AlCl_3$-EtSH. Finally it clearly appears that the structure of the substrate plays an important part in these reactions.

In order to obtain some informations about the thioalkylation we submitted **2** (R = Me, R^1 R^2 = $(CH_2)_5$) to the action of $AlCl_3$ (4.5 eq) - EtSH (60 eq). The corresponding **3** was obtained with 55 % yield.

According to Casnati and his collaborators,[4] aluminium alkoxides may be expected as intermediate. So, taking into account the demethylation mechanism,[5] we propose the mechanism given in Scheme 2 for the formation of **3**.

The driving force of these nucleophilic substitutions may be reasonably attributed to the formation of the Al-O bond.

Typical experimental procedures

Method A : 1 eq. of compound **1** diluted in CH_2Cl_2 (5 ml for 3 mmol) was added dropwise at 0°C to a mixture composed of 1.5 eq. of AlX_3 and 20 eq. of EtSH or PhSH. After the reaction was stirred one hour at 0°C, 1.5 eq. of AlX_3 and 20 eq. of EtSH or PhSH were still added. The reaction was monitored by gpc (capillary HP1, 6 m) and stopped when the maximum amount of the wished product was reached. The reaction mixture was hydrolysed with HCl 1N at 0°C, and extracted with CH_2Cl_2. The organic layer was washed with water, then with brine, dried over Na_2SO_4, and the solvent removed under vacuum. The products were isolated by flash column chromatography (Kieselgel, 40-63 μ) using eluent (AcOEt/petroleum ether) of progressive polarity (20 to 30 % for amides derivatives and 10 to 20 % for the others).

Method B : Same procedure as described for method A, but after 2 hours, a third portion of 1.5 eq. of AlX_3 and 20 eq. of EtSH or PhSH was added at 0°C and stirring was continued at room temperature for the time indicated in the Table.

2 R = Me; R^1,R^2 = -$(CH_2)_4$- : M.p. (totoli) = 92°C ; IR ν (cm^{-1}) : 3356 (OH); 2930 - 2839 (aliph). ^{1}H NMR ($CDCl_3$) δ ppm: 7.00-6.46 (m, 3 H, arom H); 6.00 (s, 1 H, OH exchanged with D_2O); 3.30 (s, 3 H, NCH_3); 2.83-2.16 (m, 4 H, 2xCH_2); 2.00-1.46 (m, 4 H, 2xCH_2). ^{13}C NMR ($CDCl_3$) δ ppm : 148.55 (C-OH); 136.48; 132.03; 127.47 (arom. C); 109.74; 108.76 (arom. C-H); 108.20 (arom. C); 102.72 (arom. C-H); 28.61 (Me); 23.00; 21.87; 20.84 (CH_2). Analysis : $C_{13}H_{15}ON$: % Calc : C 77.57; H 7.51; N 6.95. Found : C 77.45; H 7.51; N 6.86.

3 R = Me; R^1,R^2 = -$(CH_2)_4$- : M.p. (totoli) = 51°C. IR ν (cm^{-1}) : 2927 - 2840 (aliph). ^{1}H NMR ($CDCl_3$) δ ppm : 7.5-6.9 (m, 3 H, arom H); 3.5 (s, 3 H, NCH_3); 3.1-2.3 (q+m, 6 H, SCH_2 + 2 x CH_2); 2.2-1.5 (m, 4 H, 2 x CH_2); 1.5-1.0 (t, 3 H, CH_3). ^{13}C NMR ($CDCl_3$) δ ppm : 136.48 (C-SEt); 135.98; 127.71 (arom. C); 125.30 (arom. CH); 123.63 (arom. C); 122.37 (arom. CH); 108.97 (arom. C); 108.74 (arom. CH); 30.74 (S-CH_2); 28.92 (N-Me); 23.06; 21.99; 20.90 (CH_2); 14.74 ($\underline{C}H_3$-CH_2). Analysis : $C_{15}H_{19}NS$: % Calc : C 73.41; H 7.80; N 5.70; S 13.06. Found : C 73.64; H 7.95; N 5.60; S 12.91.

2 R = Me; R^1,R^2 = -$(CH_2)_5$- : M.p. (EtOAc, CH_2Cl_2, totoli) = 102°C. IR ν (cm^{-1}) : 3349 (OH); 2920-2845 (aliph). ^{1}H NMR ($CDCl_3$) δ ppm : 6.5-7.3 (m, 3 H, arom H); 5.2(s, 1 H, OH exchanged with D_2O); 3.6 (s, 3 H, NCH_3); 2.5-3.0 (m, 4 H, 2xCH_2); 1.5-2.0 (m, 6 H, 3xCH_2). ^{13}C NMR ($CDCl_3$) δ ppm : 148.8 (C-OH); 140.0; 131.3; 128.1; 112.6 (arom. C);109.7; 109.2; 102.4 (arom. CH); 31.4 (CH_2); 29.4 (Me); 28.3; 26.9; 26.2; 24.3 (CH_2). Analysis : $C_{14}H_{17}ON$: % Calc : C 78.10; H 7.96; N 6.50. Found : C 77.59; H 7.85; N 6.52.

3 R = Me; R^1,R^2 = -$(CH_2)_5$- : M.p. (totoli) = 44°C. IR ν (cm^{-1}) : 2921-2846 (aliph.).^{1} H NMR ($CDCl_3$) δ ppm : 7.60 (s, 1 H, arom H); 7.25-7.10 (m, 2 H, arom H); 3.60 (s, 3 H, NCH_3); 2.90-2.70 (q+m, 6 H, SCH_2 + 2xCH_2); 1.95-1.70 (m, 6 H, 3xCH_2); 1.30-1.15 (t, 3 H, CH_3). ^{13} C NMR ($CDCl_3$) δ ppm : 139.86 (C-SEt); 135.17; 128.25 (arom. C); 125.16 (arom. CH); 123.77 (arom. C);122.37

(arom. CH); 111.32 (arom. C); 109.10 (arom. CH); 31.46; 30.81 (CH_2); 29.55 (N-Me); 28.31; 26.93; 26.25; 24.22 (CH_2); 14.80 ($\underline{C}H_3$-CH_2). Analysis : $C_{16}H_{21}NS$: % Calc : C 74.07; H 8.16; N 5.39; S 12.36.*Found : C 74.04; H 8.16; N 5.36; S 12.40.*

2 R = Me; R^1,R^2 = -$(CH_2)_{10}$- : M.p. (totoli) = 120°C. IR ν (cm^{-1}) : 3340 (OH); 2931-2849 (aliph). ^{1}H NMR ($CDCl_3$) δ ppm : 7.20-6.50 (m, 3 H, arom H); 4.50 (s, 1 H, OH exchanged with D_2O); 3.52 (s, 3 H, NCH_3); 2.90-2.30 (m, 4 H, 2xCH_2); 2.00-0.90 (m, 16 H, 8xCH_2). ^{13}C NMR ($CDCl_3$) δ ppm : 148.62 (C-OH); 138.26; 132.41; 128.25; 111.23 (arom. C); 109.97; 108.89; 103.63 (arom. CH); 29.80 (Me); 27.75; 27.30; 25.23; 24.93; 24.58; 24.47;22.25; 22.14; 21.65; 21.55 (CH_2). Analysis : $C_{19}H_{27}ON$: % Calc : C 79.94; H 9.53; N 4.90. Found : C 80.21; H 9.63; N 4.81.

3 R = Me; R^1,R^2 = -$(CH_2)_{10}$- : M.p. (totoli) = 55°C. IR ν (cm^{-1}) : 2927- 2850 (aliph). ^{1}H NMR ($CDCl_3$) δ ppm : 7.7-6.8 (m, 3 H, arom H); 3.4 (s, 3 H, NCH_3); 3.0-2.3 (q+m, 6 H, SCH_2 + 2xCH_2); 2.0-1.7 (t+m, 19 H, CH_3 + 8xCH_2). ^{13}C NMR ($CDCl_3$) δ ppm : 137.75 (C-SEt); 136.29; 128.38 (arom. C); 125.48 (arom. CH); 123.68 (arom. C); 123.42 (arom. CH); 111.85 (arom. C); 108.74 (arom. CH); 30.78 (SCH_2); 29.75 ($\underline{C}H_3CH_2$); 28.01;27.22; 25.17; 24.99; 24.61; 24.40; 22.17; 21.62; 21.47 (CH_2); 14.75 (N-Me). X Ray diffraction data have been also collected.

2 R = Me; R^1 = CON(Bu)Ph; R^2 = H : M.p. (totoli) = 150°C. IR ν (cm^{-1}) : 3373 (OH); 2959-2871 (aliph); 1614 (C=O). ^{1}H NMR ($CDCl_3$) δ ppm : 7.4-6.5 (m, 9 H, arom H + OH exchanged with D_2O); 5.7 (s,1 H, arom H); 4.0-3.7 (m, 2 H, CH_2); 3.7 (s, 3 H, NCH_3); 1.9-1.1(m, 4 H, 2xCH_2); 1.1-0.7(m, 3 H, CH_3). ^{13}C NMR ($CDCl_3$) δ ppm : 163.7 (C=O); 149.9 (C-OH); 143.1 (C-C=O); 133.0; 132.6 (arom. C); 129.1; 127.3; 127.0 (arom. CH); 126.5 (arom. C); 114.0; 110.1; 106.0; 105.4 (arom. CH) ; 50.2 (N-CH_2); 31.4 (N-Me); 29.7; 20.0 (CH_2); 13.7 (CH_3). *Analysis : $C_{20}H_{22}O_2N_2$* : % Calc : C 74.50; H 6.87; N 8.69. Found : C 74.45; H 7.18; N 8.49.

3 R = Me; R^1 = CON(Bu)Ph; R^2 = H : IR ν (cm^{-1}) : 3060-2959-2871 (aliph); 1638(C=O). ^{1}H NMR ($CDCl_3$) δ ppm : 7.5-6.7 (m,

8 H, arom H); 5.7 (s, 1 H, arom H); 3.9 (s, 3 H, NCH_3); 4.2-3.7 (m, 2 H, CH_2); 3.0-2.5 (q, 2 H, SCH_2); 1.9-0.7 (m+t, 10 H, aliph). ^{13}C NMR ($CDCl_3$) δ ppm : 162.78 (C=O); 143.16 (C-S); 136.63; 132.96 (arom. C); 129.07; 127.28; 126.87 (arom. CH); 126.58; 125.68 (arom. C); 124.92; 109.96; 106.11 (arom. CH); 49.87 (N-CH_2); 31.43 (N-Me); 29.73; 29.60; 19.96 (CH_2); 14.44; 13.64 (CH_3). MS for $C_{22}H_{26}ON_2S$ = (M+1) = 367. Analysis : $C_{22}H_{26}ON_2S$: % Calc : C 72.09; H 7.15; N 7.64; S 8.74. Found : C 72.29; H 7.48; N 7.52; S 8.62.

2 R = H; R^1 = CON(Me)Ph; R^2 = H : M.p. (totoli) = 193°C. IR ν (cm^{-1}) : 3306 (OH, NH); 1611(C=O). ^1H NMR ($CDCl_3$/DMSO) δ ppm : 10.0 (s,1 H, NH, slight exchange with D_2O); 7.7-6.7 (m, 9 H, arom H + OH exchanged with D_2O); 5.2 (s, 1 H, arom H); 3.4 (s, 3 H, NCH_3). ^{13}C NMR ($CDCl_3$/DMSO) δ ppm : 160.71 (C=O); 149.73 (C-OH); 143.13; 129.38; 128.86 (arom. C); 128.36; 126.66; 126.48 (arom. CH); 126.40 (arom. C); 113.85; 111.32; 104.19; 103.22 (arom. CH); 37.41 (N-Me). Analysis : $C_{16}H_{14}O_2N_2$: % Calc : C 72.16; H 5.29; N 10.52. Found : C71.61; H 5.16; N 10.02.

3 R = H; R^1 = CON(Me)Ph; R^2 = H : M.p. (totoli) = 169°C. IR ν (cm^{-1}) : 3269 (NH); 2962-2925 (aliph). ^1H NMR ($CDCl_3$) δ ppm : 10.2-9.9 (s, 1 H, NH); 7.7-7.0 (m, 8 H, arom H); 5.2 (s, 1 H, arom H); 3.5 (s, 3 H, NCH_3); 3.5-3.1 (q, 2 H, SCH_2); 2.5-1.5 (t, 3 H, CH_3). ^{13}C NMR ($CDCl_3$) δ ppm : 161.92 (C=O); 143.97 (C-S); 134.54; 130.16 (arom. C); 129.90; 128.56; 128.23 (arom. C); 127.91 (arom. CH); 126.07 (arom. C); 125.50; 112.09; 106.57 (arom. CH); 38.96 (N-Me); 29.89 (S-CH_2); 14.57 ($\underline{C}H_3CH_2$). Analysis : $C_{18}H_{18}ON_2S$: % Calc. : C 69.64; H 5.84; N 9.02; S 10.32. Found : C 69.36; H 6.16; N 9.28; S 9.83.

2 R = H; R^1 = CON(Oct)Ph; R^2 = H : M.p. (totoli) = 160°C. IR ν (cm^{-1}) : 3402 (OH); 3275 (NH); 2929-2850 (aliph); 1615(C=O). ^1H NMR($CDCl_3$) δ ppm : 10.3 (s, 1 H, NH slight exchange with D_2O); 7.6-6.5 (m, 9 H, arom H + OH exchanged with D_2O); 5.1 (s, 1 H, arom H); 4.0-3.6 (m, 2 H, CH_2); 1.9-0.6 (m, 15 H, aliph). ^{13}C NMR ($CDCl_3$) δ ppm : 161.53 (C=O); 147.76 (C-OH); 142.66;

130.76; 130.65 (arom. C); 129.78; 128.94; 128.48 (arom. CH); 128.28 (arom. C); 115.15; 112.28; 106.15; 105.60 (arom. CH); 51.05 (N-CH_2); 31.77; 29.35; 29.20; 27.61; 26.91; 22.60 (CH_2); 14.04 (CH_3). Analysis : $C_{23}H_{28}O_2N_2$: % Calc. C 75.78; H 7.74; N 7.68. Found : C 76.06; H 7.76; N 7.70.

3 R = H; R^1 = CON(Oct)Ph; R^2 = H : M.p. (totoli) = 87°C. IR ν (cm^{-1}) : 3277 (NH); 2952; 2930; 2853 (aliph); 1615 (C=O). ^1H NMR ($CDCl_3$) δ ppm : 10.2 (s,1 H, NH); 7.9-6.9 (m, 8 H, arom H); 5.2 (s, 1 H, arom H); 4.2-3.7 (m, 2 H, CH_2); 3.1-2.6 (q, 2 H, SCH_2); 2.2-0.7 (t + m, 18 H, aliph). ^{13}C NMR ($CDCl_3$) δ ppm : 161.56 (C=O); 142.62; 134.67 (arom. C); 130.45; 129.78; 128.86; 128.47 (arom. CH); 128.26; 125.97 (arom. C); 125.54; 112.14; 106.39 (arom. CH); 51.17 (N-CH_2); 31.72; 29.96; 29.32; 29.19; 27.58; 26.93; 22.53 (CH_2); 14.59 ($\underline{C}H_3CH_2$); 13.98 (CH_3). Analysis : $C_{25}H_{32}ON_2S$: % Calc : C 73.48; H 7.89; N 6.85; S 7.84. Found : C 73.23; H 7.83; N 6.89; S 8.09.

Acknowledgement

We thank ADIR for financial support.

References

1. Bhatt, M.V. ; Kulkarni, S.U. *Synthesis*, **1983**, 249-282 ; Akiyama, T. ; Hirofuji, H. ; Ozaki, S. *Bull. Chem. Soc. Jpn*, **1992**, *65*, 1932-1938 ; Asero Von, B. ; Colo, V. ; Erspamer, V. ; Vercellone, A. *Justus Liebigs Ann. Chem.*, **1952**, *5*, 69-74.
2. Niwa, H. ; Hida, T. ; Yamada, K. *Tetrahedron Lett.*, **1981**, *22*, 4239-4240 ; McOmie, J.P.W. ; West, D.E. *Organic Syntheses*, Collective Vol. p. 412 ; Simon, C. ; Hosztafi, S. ; Makleit, S. ; Berenyi, S. *Synth. Commun.*, **1991**, *21*, 2309-2316.

3. a) Node, M. ; Nishide, K. ; Fuji, K. ; Fujita, E. *J. Org. Chem.*, **1980**, *45*, 4275-4277 ; b) Node, M. ; Nishide, K. ; Sai, M. ; Ichikawa, K. ; Fuji, K. ; Fujita, E. *Chem. Lett.*, **1979**, 97-98.

4. Sartori, G. ; Maggi, R. ; Bigi, I. ; Arienti, A. ; Casnati, G. ; *J. Chem. Soc. Perkin Trans I*, **1993**, 39-42.

5. Node, M. ; Hori, H. ; Fujita, E. *J. Chem. Soc. Perkin Trans I*, **1976**, 2237-2240.

(Received in the UK 22 November 1993)