Synthesis of 3-amino-thiochromanes from 4-benzyl 2-thiazolines, *via* an unprecedented intramolecular electrophilic aromatic substitution†

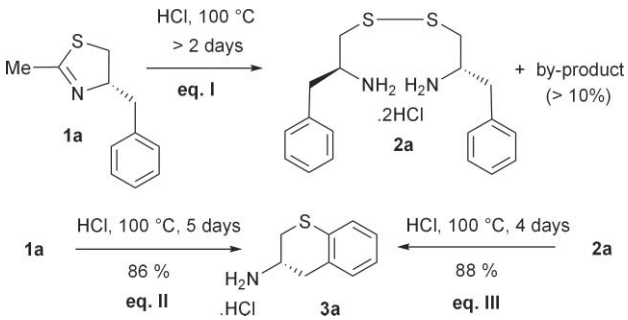
Guillaume Mercey,[a] Remi Legay,[a] Jean-François Lohier,[a] Jana Sopkova-de Oliveira Santos,[b] Jocelyne Levillain,[a] Annie-Claude Gaumont[a] and Mihaela Gulea*[a]

Received 17th February 2010, Accepted 7th April 2010
First published as an Advance Article on the web 22nd April 2010
DOI: 10.1039/c003050c

A one-pot synthesis of various *N*-substituted 3-amino-thiochromanes from 4-benzyl-2-methyl thiazoline *via* a thiazolinium salt is described. The obtained 3-amino-thiochromanes are enantiopure, as their precursors derive from chiral 2-aminoalcohols. The reaction involves the formation of a disulfide, which subsequently takes part in an unprecedented intramolecular electrophilic aromatic substitution.

3-Amino-thiochromanes have been described in several publications[1] and patents[2] as compounds with interesting therapeutic activities. They have been studied for their ability to act on the central nervous system receptors,[1a,c,2b,e] and as antihypertensive[1b,2a,c] or cardiovascular agents.[2d] Only a few synthetic routes for their preparation have been published, and all involve a 1,4-addition of a thiophenol derivative to a Michael acceptor and subsequent cyclisation into thiochromane.[2b,3] In all the reported syntheses, the amino function is not present in the starting material, but brought after cyclisation by transformation of another functional group such as an oxime,[3c] a carboxylate,[2b] or a nitro.[3a] Alternative methods to prepare 3-amino-thiochromanes, especially in enantiopure form,[3a] are still lacking.

Recently, we described the synthesis of β-aminothiols or their disulfides from β-aminoalcohols and methyldithioacetate, *via* the acidic hydrolysis of a thiazoline or a thiazolinium salt.[4] When thiazoline (*S*)-**1a** (derived from commercial L-phenylalaninol) was subjected to acid hydrolysis (at 100 °C, in aqueous 5M HCl) in air to access disulfide **2a**, the formation of a by-product was observed, in particular when the heating time was longer than 2 days (Scheme 1, eq. I). Therefore, we repeated the experiment by prolonging the reaction time and, after 5 days, a full conversion into the unknown product was obtained. After isolation, the product was analysed by NMR and mass spectroscopy and identified as the 3-amino-thiochromane **3a** (Scheme 1, eq. II). The yield was 86%. Very probably, this transformation took place *via* an aromatic electrophilic substitution involving disulfide **2a**, which is first



Scheme 1 Synthesis of 3-amino-thiochromane **3a**.

formed by hydrolysis of **1a** and then generates a sulfenium cation by protonation with HCl. Indeed, when pure disulfide **2a** was submitted to the acidic hydrolysis, compound **3a** was obtained in 88% yield, after 4 days of heating (Scheme 1, eq. III). This result highlights an unprecedented intramolecular electrophilic aromatic substitution. Only a few examples of aromatic electrophilic substitution involving a disulfide are reported,[5] and, to the best of our knowledge, no intramolecular version has been mentioned.

A single crystal of **3a** was isolated and analysed by X-ray diffraction and the absolute configuration was determined to be (*S*), the same as that of its precursor, the thiazoline **1a**. The opposite enantiomer (*R*)-**3a** was also synthesized and its structure confirmed by X-ray analysis (Fig. 1).

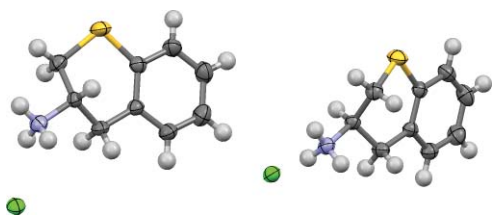
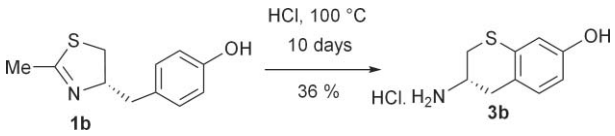


Fig. 1 Crystal structures of (*S*)-**3a** (at left) and (*R*)-**3a** (at right).

A second experiment was attempted to synthesize the 3-amino-7-hydroxy-thiochromane **3b** starting from thiazoline **1b**. The latter was accessible from commercial (*S*)-tyrosinol by using our described procedure.[4a] Placed under similar acidic hydrolysis conditions, thiazoline **1b** led after 10 days to a mixture of disulfide and thiochromane (1 : 2 ratio). After several washings of the crude product with acetone, pure thiochromane **3b** was isolated in 36% yield (Scheme 2). When the *O*-mesylated derivative of thiazoline **1b** was used as the starting material, a complete conversion into the corresponding disulfide was observed, however, even after 20 days of heating under acidic conditions, no trace of the corresponding thiochromane was detected. This is probably due to the presence of

[a]*Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, INC3M, FR 3038, ENSICAEN, Université de Caen Basse-Normandie, 6, Bd. Maréchal Juin, 14050, Caen, France. E-mail: mihaela.gulea@ensicaen.fr; Fax: 33 23145 2877; Tel: 33 23145 2898*
[b]*Laboratoire de Crystallographie, Centre d'Etudes et de Recherche sur le Médicament de Normandie, EA 4258, FR CNRS 3038 INC3M, Université de Caen Basse-Normandie, Bd. Becquerel, 14032, Caen*

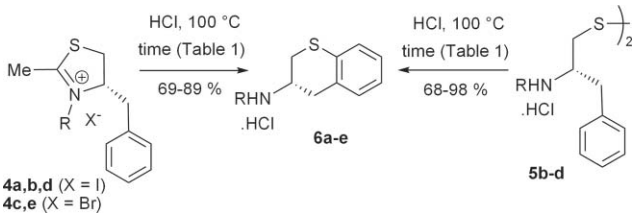
† Electronic supplementary information (ESI) available: Experimental, spectral data, NMR spectra for compounds **3a**,**b** and **6a–e**, crystal data for (*S*)-**3a** and (*R*)-**3a**. CCDC reference numbers 766389 and 766390. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c003050c



Scheme 2 Synthesis of 3-amino-7-hydroxy-thiochromane **3b**.

the mesylate substituent, which should lower the electron density of the aromatic ring and disfavour the electrophilic aromatic substitution.

Then, we examined the possibility of extending the method to the synthesis of 3-amino-thiochromanes possessing a secondary amino function using thiazolinium salts[6] as precursors. The required thiazolinium salts are easily accessible by *N*-alkylation of **1a** and were prepared according to our described procedure.[4b] First, we prepared *N*-methyl thiazolinium iodide **4a**, and then we placed it in the same reaction conditions as used previously (Scheme 3). After 5 days of heating in 5 M aqueous HCl, the expected *N*-methyl 3-amino-thiochromane **6a** was obtained in 69% yield (Table 1, entry 1). This result shows that it is possible to access variously *N*-substituted 3-amino-thiochromanes from thiazolinium salts, in a one-pot reaction. Thus, several thiazolinium salts (**4b–e**), bearing simple alkyl or functionalized substituents, were prepared and reacted under similar conditions (Scheme 3, Table 1, entries 2–5). In all cases, the corresponding thiochromanes were obtained after a rather long reaction time (5–14 days), although in excellent yields (82 to 89%). To confirm once again that the reaction takes place through a disulfide intermediate, three of these thiochromanes, **6b**, **6c** and **6d**, were also synthesised from the disulfides precursors **5b–d**, respectively (Scheme 3, Table 1, entries 6–8). The obtained yields were similar to those obtained starting from the thiazolinium salts. As expected, the reaction time was a little shorter (3, 6 and 4 days *vs.* 5, 14 and 6 days, respectively), as an additional time is necessary to transform the thiazolinium salt into the disulfide.



Scheme 3 Synthesis of *N*-substituted 3-amino-thiochromanes **6a–e**.

In conclusion, a new method to synthesize 3-amino-thiochromanes bearing a primary amino group from 4-benzyl thiazolines was found. The method was successfully extended to the preparation of secondary amino-thiochromanes derivatives from thiazolinium salts, which are versatile precursors enabling easy structural variation. All the obtained 3-amino-thiochromanes are enantiopure (derived from L-phenylalaninol for **3a**, **6a–e**, or *S*-tyrosinol for **3b**). This one-pot synthesis requires very simple conditions (heating in aqueous 5 M HCl), and involves two steps:

Table 1 Synthesis of *N*-substituted 3-amino-thiochromane **6a–e**

Entry	R	Starting material	Time/days	Product	Yield (%)
1	Me	**4a**	5	**6a**	69
2	Bu	**4b**	5	**6b**	87
3	Bn	**4c**	14	**6c**	89
4	CH_2CO_2Et[a]	**4d**	6	**6d**	83
5	CH_2CH_2OH	**4e**	7	**6e**	82
6	Bu	**5b**	3	**6b**	84
7	Bn	**5c**	6	**6c**	98
8	CH_2CO_2H	**5d**	4	**6d**	68

[a] In the starting thiazolinium salt R = CH_2CO_2Et and in the product R = CH_2CO_2H, as a result of the ester hydrolysis.

the formation of a disulfide and a subsequent intramolecular cyclisation. The last step is an interesting example of intramolecular electrophilic aromatic substitution, which merits further investigations.

Acknowledgements

The "Ministère de la Recherche et des Nouvelles Technologies" (grant for GM), the "Région Basse-Normandie", the CNRS (Centre National de la Recherche Scientifique), and the European Union (FEDER funding) are acknowledged for the financial support.

Notes and references

1 (*a*) L. A. van Vliet, N. Rodenhuis, D. Dijkstra, H. Wikström, T. A. Pugsley, K. A. Serpa, L. T. Meltzer, T. G. Heffner, L. D. Wise, M. E. Lajiness, R. M. Huff, K. Svensson, S. Sundell and M. Lundmark, *J. Med. Chem.*, 2000, **43**, 2871; (*b*) B. K. Trivedi, C. J. Blankley, J. A. Bristiol, H. W. Hamilton, W. C. Patt, W. J. Kramer, S. A. Johnson, R. F. Bruns, D. M. Cohen and M. J. Ryan, *J. Med. Chem.*, 1991, **34**, 1043; (*c*) A. Beliaev, D. A. Learmonth and P. Soares-da-Silva, *J. Med. Chem.*, 2006, **49**, 1191.

2 (*a*) A. J. Hutchison and J. E. Francis, Eur. Pat. Appl. (1989), EP 323807 A2 19890712; (*b*) A. J. Hutchison, *Eur. Pat. Appl.*, 1988, EP 280269 A1 19880831; (*c*) B. Trivedi, *Eur. Pat. Appl.*, 1986, EP 181109 A2 19860514; (*d*) P. Soares-da-Silva, *PCT Int. Appl.*, 2008, WO 2008085074 A2 20080717; (*e*) L. G. Larsson, R. Noreen, L. A. Renyi, S. B. Ross, D. D. Sohn, B. E. Svensson and S. O. Thorberg, *PCT Int. Appl.*, 1991, WO 9109853 A1 19910711.

3 (*a*) R. Dodda, J. J. Goldman, T. Mandal, C.-G. Zhao, G. A. Broker and E. R. T. Tiekink, *Adv. Synth. Catal.*, 2008, **350**, 537; (*b*) J. Wang, H. Xie, H. Li, L.-S. Zu and W. Wang, *Angew. Chem., Int. Ed.*, 2008, **47**, 4177; (*c*) R. Bognár, M. Rákosi and J. Bálint, *Tetrahedron Lett.*, 1964, **5**, 137.

4 (*a*) G. Mercey, D. Brégeon, A.-C. Gaumont, J. Levillain and M. Gulea, *Tetrahedron Lett.*, 2008, **49**, 6553; (*b*) G. Mercey, J.-F. Lohier, A.-C. Gaumont, J. Levillain and M. Gulea, *Eur. J. Org. Chem.*, 2009, 4357.

5 (*a*) B. S. Farah and E. E. Gilbert, *J. Org. Chem.*, 1963, **28**, 2807; (*b*) P. F. Ranken and B. G. McKinnie, *J. Org. Chem.*, 1989, **54**, 2985; (*c*) Q. T. Do, D. Elothmani and G. L. Guillanton, *Tetrahedron Lett.*, 1998, **39**, 4657; (*d*) R. S. Glass, V. V. Jouikov and N. V. Bojkova, *J. Org. Chem.*, 2001, **66**, 4440; (*e*) R. S. Glass and V. V. Jouikov, *Tetrahedron Lett.*, 1999, **40**, 6357; (*f*) H. Behringer and K. Kuchinka, *Angew. Chem.*, 1960, **72**, 348.

6 (*a*) J. Levillain, G. Dubant, I. Abrunhosa, M. Gulea and A.-C. Gaumont, *Chem. Commun.*, 2003, 2914; (*b*) D. Brégeon, J. Levillain, F. Guillen, J.-C. Plaquevent and A.-C. Gaumont, *Amino Acids*, 2008, **35**, 175; (*c*) D. Brégeon, J. Levillain, F. Guillen, J.-C. Plaquevent and A.-C. Gaumont, *ACS Symposium Series*, Oxford Press, vol. 950, 2007, chap. 19, pp 246–258.