Tetrahedron Letters 50 (2009) 6466–6468

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective one-pot synthesis of highly differently substituted thiochromans

Andrea Seifert, Rainer Mahrwald *

Institute of Chemistry, Humboldt-University Berlin, Brook-Taylor Str. 2, 12489 Berlin, Germany

ARTICLE INFO

Article history:
Received 17 July 2009
Revised 26 August 2009
Accepted 1 September 2009
Available online 6 September 2009

ABSTRACT

A highly stereoselective one-pot procedure to anti-configured thiochromans is described. This reaction functions at room temperature in the presence of catalytic amounts of trifluoroacetic acid. The transformation gives a selective but optional access to highly substituted thiochromans, which have been not attainable until now.

Different substituted thiochromans are of considerable interest because many of them possess important biological activities.[1] Moreover, there are several thiochromans that are active in the treatment of lipoxygenase-mediated disorders,[2] functional gastrointestinal disorders (e.g., functional dyspepsia),[3] irritable bowel syndrome (IBS),[4] and in the therapeutic treatment of neurological disorders.[5] They proved to be sufficiently high estrogen pure antagonist through oral administration,[6] acetyl cholinesterase inhibitors (approved in 2000 for the treatment of Alzheimer disease),[7] and dopamine D3 receptor-selective agonists.[8] Thiochromans inhibit the HIV-1 replication in H9 lymphocytes.[9]

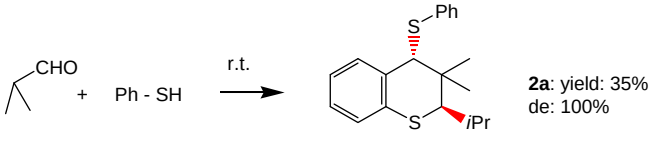
For the synthesis of thiochromans (4-thioaryl-2,3,4-trihydro-1-benzothiopyran) several general methods are known. The classical approach is the thio-Claisen rearrangement of the corresponding allyl phenyl sulfides.[10] An access to more substituted thiochromans can be achieved by an intramolecular electrophilic aromatic substitution of corresponding aryl thioethers.[11] This transformation was extended to a one-pot procedure involving the generation of the starting aryl thioethers. This implies a 1,4-addition of arylthiols to a conjugated system, followed by an electrophilic cyclization of a carbenium intermediate in the presence of Bronsted or Lewis acids.[12] Also, asymmetric and organocatalytic Michael-aldol processes based on the use of 2-mercaptobenzaldehyde were developed. α,β-Unsaturated carbonyl compounds were treated with 2-mercaptobenzaldehyde in the presence of several different chiral organocatalysts. These transformations were carried out with α,β-unsaturated aldehydes,[13] enones,[14] nitro olefins,[15] unsaturated imides,[16] maleinimides,[17] and benzylidenemalonates.[18] Based on these reactions, the desired construction of different substituted quaternary carbon centers at C3 is not possible.

In this Letter we describe a catalytic and stereoselective one-pot procedure that overcomes this void for the synthesis of C3-substituted thiochromans. During our ongoing studies on the use of $LiClO_4$ in C–C bond formation processes of alcohols[19] we also tested thiols in these reactions. By the deployment of thiophenols we observed a highly stereoselective formation of thiochromans in the presence of catalytic amounts of carboxylic acids (Scheme 1).

In order to test the scope and limitation of this transformation we started systematic investigations of the model reaction of Scheme 1. The reactions were carried out at room temperature for 12 h. First, we examined the influence of additives in these reactions. Several other lithium salts (LiCl, LiBr, LiJ) and metal perchlorates ($NaClO_4$, $KClO_4$, $Mg(ClO_4)_2$) were tested. A reaction could not be detected for any of these additives. However, a reaction occurs in the presence of $LiClO_4$. This result underlines once again the exceptional position of $LiClO_4$ as an additive.[20] Also, several Bronsted acids were explored with regard to their utility in these reactions. Trifluoroacetic acid (10 mol %) proved to be the optimal catalyst among other acids we tested.[21]

Under optimized reaction conditions, the results are as follows:Thiochromans **2a**–**e** were isolated in moderate yields when used with aldehydes. The yields were increased considerably by deployment of trioxanes—stable and more reactive intermediates of the corresponding aldehydes. The results of this series are shown in Table 1. Thiochromans **2a**–**e** were isolated with exceptionally high anti-selectivities (with the exception of **2c**).

Next, we explored cross-coupling reactions. We conducted different trioxanes of enolizable aldehydes under the reaction conditions described above. The corresponding thiochromans **2e**–**g** were isolated in moderate to good yields (Table 2). As before, extremely



Scheme 1. Aldol/cyclization reaction to thiochromans. Reaction conditions: 100 mol % $LiClO_4$, 1 mol % CF_3CO_2H.

* Corresponding author.
E-mail address: rainer.mahrwald@rz.hu-berlin.de (R. Mahrwald).

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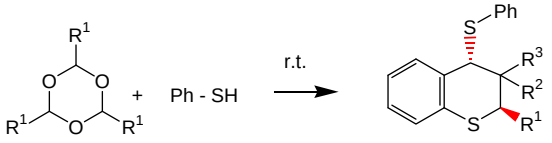
doi:10.1016/j.tetlet.2009.09.009

Table 1
Homo-aldol coupling/cyclization of thiochromans **2a–d**[a]

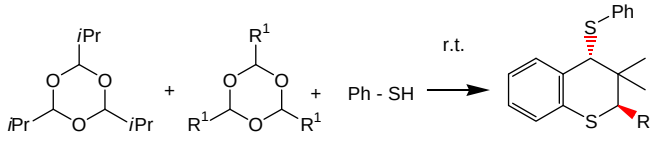


1a-d **2a-d**

Entry	Compound	Yield (%)	*Anti*/*syn*[b]
1	**2a**: R1–*i*Pr, R2 = R3–Me	61	100/0
2	**2b**: R1–Cy, R2 = R3–C_5H_{10}	39	100/0
3	**2c**: R^1–$(CH)_2$Ph, R^2–Ph–CH_2, R^3–H	48	75/25[c]
4	**2d**: R^1–Me, R^2 = R^3–H	27	100/0

[a] Reaction conditions: 100 mol % $LiClO_4$, 1 mol % CF_3CO_2H.
[b] Configurations of thiochromans were determined by a combination of single-crystal X-ray analysis, NMR correlations, NOE experiments and reasonable analogy; see Supplementary data.
[c] For determination of this ratio, see Supplementary data.

Table 2
Cross-coupling/cyclization reactions[a]



1b,c,e **2e-g**

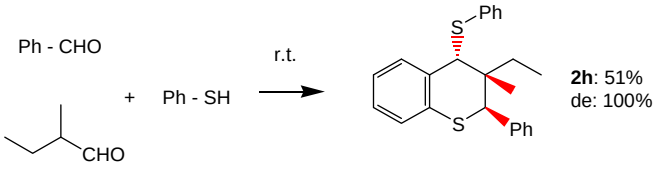
Entry	Compound	Yield (%)	*Anti*/*syn*
1	**2e**: R^1–Cy	34	100/0
2	**2f**: R^1–$(CH_2)_2$Ph	51	100/0
3	**2g**: R^1–Ph	77	100/0

[a] Reaction conditions: 100 mol % $LiClO_4$, 1 mol % CF_3CO_2H.

high anti-selectivities were detected. Moreover, high chemoselectivities were observed. This reagent system ($LiClO_4$/CF_3CO_2H) strongly differentiates between carbonyl reactivities of enolizable trioxanes employed under these reaction conditions. Isobutyraldehyde acts as the ene-component during the aldol process in compounds **2e** and **2f**. No other possible regioisomers could be detected.

A temporary highlight in this series represents the following cross aldol/cyclization reaction. Benzaldehyde and 2-methylbutyraldehyde were reacted with thiophenol in the presence of $LiClO_4$ and catalytic amounts of trifluoroacetic acid. Highly different substituted thiochroman **2h** could be isolated in 51% yield as a single stereoisomer (Scheme 2).

In summary, we have developed a very useful method for the construction of stereogenic centers of thiochromans. Comparable thiochromans, with such a substitution pattern are not accessible by previously known methods.



Scheme 2. Cross-coupling/cyclization of benzaldehyde and 2-methyl-butyraldehyde. Reaction conditions: 100 mol % $LiClO_4$, 1 mol % CF_3CO_2H.

Although a detailed reaction mechanism remains ambiguous, the following multistep sequence can be assumed: an aldol addition of enolizable aldehydes in the presence of thiophenol, followed by an electrophilic cyclization of a cationic species. These considerations are supported by experiments of isolated β-hydroxyaldehydes with thiophenol in the presence of catalytic amounts of trifluoroacetic acid. In these reactions we obtained the corresponding thiochromans in high yields and stereoselectivities. Further investigations of reaction mechanism and enantioselective execution of this reaction are underway.

Acknowledgments

The authors thank Deutsche Forschungsgemeinschaft, Bayer-Schering Pharma AG, Bayer Services GmbH, BASF AG, and Sasol GmbH for financial support. P. Neubauer and B. Ziemer are gratefully acknowledged for single-crystal X-ray structure analyses.

Supplementary data

General procedures for the synthesis of thiocromans and characterizations of all reaction products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.009.

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