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Facile synthesis of spiro chromanone-tetrahydrothiophenes with three contiguous stereocenters via sulfa-Michael/aldol cascade reactions

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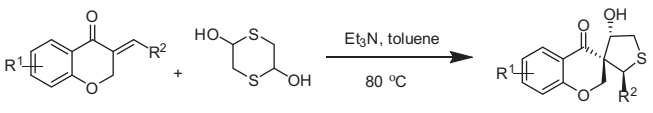
ABSTRACT

A novel sulfa-Michael/aldol cascade reaction of (*E*)-3-arylidenechroman-4-ones with 1,4-dithiane-2,5-diol has been developed. This method provides a new practical and facile approach to 4′-hydroxy-2′-aryl-4′,5′-dihydro-2′*H*-spiro[chroman-3,3′-thiophen]-4-ones with three contiguous stereocenters in high yields. The transformation is atom-economic with good to excellent diastereoselectivities.

Spiro heterocycles constitute a structurally unique class of natural and pharmacological molecules. They have attracted a great deal of attention due to their interesting conformational features and wide spectrum of biological activities.[1] As valuable synthetic targets, the construction of this structure is both attractive and challenging in the synthetic community.[2] Among many spiro heterocycles, spiro chromanone analogues are found in many biological, natural and synthetic products, and they often show a broad range of favourable properties, such as antitumor,[3] antimicrobial,[4] Acetyl-CoA carboxylase (ACC) inhibiting activities[5] and inhibition of human telomerase.[6] As a consequence, the interest in their synthesis has significantly intensified over the past few decades.[7] Moreover, tetrahydrothiophenes, especially the polysubstituted tetrahydrothiophenes, are also important units of many natural products and pharmaceutical agents, such as essential coenzyme biotin with important biological functions,[8] chiral organocatalyst,[9] potential inhibitors of HIV,[10] glucosidase inhibitors,[11] antitumor natural product[12] and human A3 adenosine receptor ligands.[13] In view of the importance of the two types of heterocycles, it is rational to envisage that a combination of the two privileged motifs in a spiro structure may bring out some advantages to assemble drug-like molecules.[2c,7a]

Recently, much progress has been reported towards highly functionalized tetrahydrothiophene analogues from commercially available 1,4-dithiane-2,5-diol (the dimer of 2-mercaptoacetaldehyde) and α,β-unsaturated compounds via tandem sulfa-Michael/aldol condensation reaction in a one-pot manner.[14] Based on these precedents, we envisaged that Michael addition of 2-mercaptoacetaldehyde to (*E*)-3-arylidenechroman-4-ones followed by intramolecular aldol reaction would generate highly functionalized spiro chromanone-tetrahydrothiophenes. In continuation of our research interest in developing new methodologies towards novel structures via the cascade process,[15] herein we describe the preparation of a new family of spiro chromanone-tetrahydrothiophenes with three contiguous stereocenters in high yields and diastereoselective manners via sulfa-Michael/aldol cascade reaction. (Scheme 1).

Initially, (*E*)-3-arylidenechroman-4-one derivatives were prepared by condensation of appropriate chroman-4-ones and various



Scheme 1. General synthesis of spiro chromanone-tetrahydrothiophenes.

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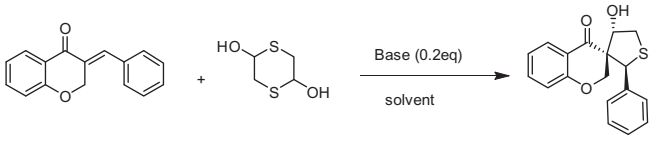
Table 1
Screening of reaction conditions

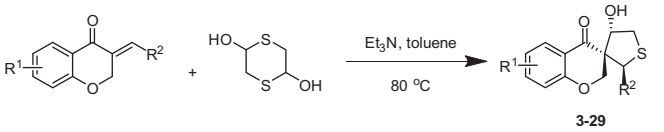


1 2 3

Entry[a]	Base	Solvent	T (°C)	t (h)	Yield[b] (%)	dr[c]
1	Et_3N	Toluene	rt	6	70	90:10
2	Et_3N	DCM	rt	3	40	71:29
3	Et_3N	DMF	rt	3	66	82:18
4	Et_3N	EtOH	rt	2	65	86:14
5	Et_3N	CH_3CN	rt	2	68	88:12
6	Et_3N	THF	rt	12	46	89:11
7	DIPEA	Toluene	rt	11	68	85:15
8	DABCO	Toluene	rt	8	62	83:17
9	DBU	Toluene	rt	7	66	81:19
10	DMAP	Toluene	rt	7	59	82:8
11	Pyrrolidine	Toluene	rt	10	65	83:17
12	Piperidine	Toluene	rt	9	55	85:15
13	K_2CO_3	Toluene	rt	6	58	89:11
14	NaOAc	Toluene	rt	6	57	86:14
15	Et_3N	Toluene	40	5	75	97:3
16	Et_3N	Toluene	60	3	87	99:1
17	**Et_3N**	**Toluene**	**80**	**1**	**95**	**98:2**
18	Et_3N	Toluene	100	1	92	92:8
19[d]	Et_3N	Toluene	80	1	95	95:5
20[e]	Et_3N	Toluene	80	2	84	97:3

The bold entry is the optimized condition for the reaction.
[a] Unless otherwise specified, the reactions were carried out with **1** (0.2 mmol), **2** (0.1 mmol), base (20 mol %), in the solvent (1 mL).
[b] Isolated yield of the isomers.
[c] Determined by ^1H NMR analysis of the crude mixture.
[d] 30 mol % catalyst was used.
[e] 10 mol % catalyst was used.

Table 2
Scope of Sulfa-Michael/aldol cascade reaction



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Entry[a]	R^1	R^2	Product	t (min)	Yield[b] (%)	dr[c]
1	H	Ph	**3**	60	95	98:2
2	H	4-MeC_6H_4	**4**	80	93	98:2
3	H	3-MeC_6H_4	**5**	40	93	85:15
4	H	2-MeC_6H_4	**6**	50	94	84:16
5	H	4-$iPrC_6H_4$	**7**	90	90	96:4
6	H	4-FC_6H_4	**8**	40	96	96:4
7	H	3-FC_6H_4	**9**	30	98	99:1
8	H	2-F C_6H_4	**10**	40	97	98:2
9	H	4-ClC_6H_4	**11**	30	99	93:7
10	H	3-ClC_6H_4	**12**	40	96	92:8
11	H	2-ClC_6H_4	**13**	30	96	87:13
12	H	4-BrC_6H_4	**14**	30	95	96:4
13	H	4-OHC_6H_4	**15**	100	85	86:14
14	H	4-$MeOC_6H_4$	**16**	120	89	98:2
15	H	3-$MeOC_6H_4$	**17**	50	95	92:8
16	H	2-$MeOC_6H_4$	**18**	50	93	98:2
17	H	4-OH,3$MeOC_6H_3$	**19**	40	96	89:11
18	H	3,4,5-Tri-$MeOC_6H_2$	**20**	40	94	88:12
19	H	4-$NMe_2C_6H_4$	**21**	100	83	96:4
20	H	2-Furyl	**22**	40	90	95:5
21	H	2-Thienyl	**23**	50	93	94:6
22	H	3-Thienyl	**24**	50	96	93:7
23	H	2-Pyridyl	**25**	80	88	92:8
24	H	2-naphthyl	**26**	30	98	93:7
25	H	PhCH=CH—	**27**	50	97	93:7
26	6-Me	Ph	**28**	80	87	95:5
27	6-Cl	Ph	**29**	40	88	76:24

[a] All reactions were carried out in toluene (1 mL) with various (*E*)-3-arylidenechroman-4-ones (0.2 mmol), **2** (0.1 mmol) in the presence of 20 mol % Et_3N at 80 °C.
[b] Isolated yield of the isomers.
[c] Determined by ^1H NMR analysis of the crude product.

substituted benzaldehydes following the reported procedure.[16] Next, 1,4-dithiane-2,5-diol **2** and (*E*)-3-benzylidenechroman-4-one **1** were chosen as reactants for screening reaction conditions and the results are summarized in Table 1. We were pleased to find that the reaction with 20 mol % Et_3N in toluene at rt for 6 h proceeded as expected affording the spirocyclic product **3a** in 70% yield and 90:10 diastereoselectivity (Table 1, entry 1). The mixture of diastereomers was inseparable and the ratio was determined by integration of characteristic signals in ^1H NMR spectra of the crude product. Encouraged by this promising result, we attempted to test the effect of various solvents including dichloromethane, dimethyl formamide, ethanol, acetonitrile and tetrahydrofuran. These experiments revealed that the domino reaction could be carried out in various protic and aprotic solvents with low to moderate conversions and moderate to good diastereoselectivities (Table 1, entries 2–6), and toluene might be the best suitable solvent in terms of both reactivity and selectivity. With the optimized solvent in hand, we further investigated the effect of different bases to enhance the efficiency of the reaction. Unfortunately, the attempt did not work efficiently (Table 1, entries 7–14). However, to our delight, the reaction went smoothly and furnished the desired product in much shorter time with significantly higher yield and better diastereoselectivity when the temperature was elevated (Table 1, entries 15–18). Subsequently, increasing loading of catalyst had little impact on the efficiency of the reaction (Table 1, entry 19), whereas reducing the catalyst loading decreased the yield and prolonged the reaction time (Table 1, entry 20). Thus, the best condition was achieved when the reaction was performed at 80 °C and the loading of the catalyst Et_3N was maintained at 20 mol % (Table 1, entry 17).

Having established the best protocol for the reaction, we decided to explore the scope and generality of this domino reaction and the results are outlined in Table 2.[17] In all the cases, the reaction was completed in two hours, affording the corresponding spirocyclic products in generally good to excellent yields (up to 99%) and high levels of diastereoselectivity (up to 99:1). Various electron-withdrawing and electron-donating substituents were appended to the benzene ring of the benzylidene-chroman-4-ones, and it was revealed that the reaction could go smoothly to give the desired products in 83–99% yields and 86:14 dr to 99:1 dr (Table 2, entries 2–19). Notably, satisfying results were also achieved with the arylidene-chroman-4-one bearing heteroaromatic rings (Table 2, entries 20–23). Sterically hindered naphthyliene-chroman-4-one was also compatible with the reaction conditions (Table 2, entry 24). Additionally, alkenylidene chroman-4-ones derived from cinnamaldehyde could also be utilized as a suitable reactant in the cascade sulfa-Michael/aldol reaction to furnish the desired product while no 1,6-adduct was detected (Table 2, entry 25). Furthermore, 6-Me and 6-Cl substituted benzylidene chroman-4-ones were also examined and turned out to be tolerated in the reaction. However, the 6-Cl substituted substrate gave lower diastereoselectivity compared to the latter (Table 2, entries 26-27).

The structures of 4′-hydroxy-2′-aryl-4′,5′-dihydro-2′*H*-spiro[chroman-3,3′-thiophen]-4-ones were characterized by ^1H NMR, ^{13}C NMR and HRMS studies. The relative configuration of the product was confirmed by HMBC correlations and ROESY correlations as illustrated for compound **3** as a representative example