Tetrahedron 70 (2014) 2257–2263

Contents lists available at ScienceDirect

Tetrahedron

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

One-pot synthesis of multifunctionalized cyclopropanes

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ARTICLE INFO

Article history:
Received 21 November 2013
Received in revised form 5 February 2014
Accepted 13 February 2014
Available online 18 February 2014

Keywords:
Cyclopropanes
Sulfones
Chalcones
Benzaldehydes
Ketones
Annulation

ABSTRACT

A facile one-step synthetic protocol toward multifunctionalized cyclopropanes **4** is developed from substituted chalcones **1** and sulfones **2** in good yields via a [2C+1C] annulation.

1. Introduction

A cyclopropane unit is a three-membered ring with a small and highly strained motif that forms the core structure of a large family of natural products and many pharmacological agents with important biological activities and interesting structural properties.[1] The formation of a cyclopropane unit, based upon the activation of electron-deficient olefins, has been accomplished using transition metal promoted routes.[2] Compared to literature reports, the Michael-initiated ring-closure procedures, using α-diazonium,[3] sulfur ylide,[4] α-pyridinium,[5] α-halo,[6] or α-arsonium[7] carbonyls (one-carbon synthon), are attractive alternatives to control the specific stereochemistry for the synthesis of multifunctionalized cyclopropanes. To continue our recent investigation of the Claisen–Schmidt condensation for the synthesis of multifunctionalized molecules (e.g., cyclohexanes, *m*-terphenyls, benzo[*g*]indazoles, azahomoisotwistanes, and oxtanes),[8] a stereochemical, high-yield, easy-operation route for NaH-mediated synthesis of 1,2,3-trisubstituted cyclopropanes was studied next (Fig. 1).

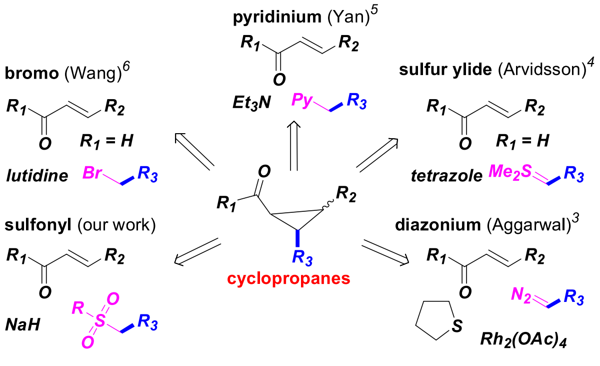

Fig. 1. Synthetic routes of cyclopropanes.

2. Results and discussion

To initiate the synthetic work, several chalcones **1** were prepared in nearly quantitative yields according to our recent literature methods from NaOH-mediated Claisen–Schmidt condensation of substituted methyl ketones with arylaldehydes under a methanolic refluxing solution.[8] Next, synthesis of benzyl sulfones **2** was achieved from nucleophilic substitution of substituted benzylic bromide with sodium sulfinates (**3**, RSO_2Na) in good yields. In an attempt to develop a practical protocol of multifunctional cyclopropane **4a** with the adjacent *cis*-diphenyl substituents, a NaH-mediated one-pot [2C+1C] synthetic route of the starting chalcone **1a** (R_1=R_2=Ph) with benzyl sulfone **2a** in refluxing THF provided cyclopropane **4a** at an 80% yield, as shown in Scheme 1. For Michael-initiated ring-closure approaches, this present protocol is a novel route to achieve the formation of a three-membered ring via a one-carbon synthon with a sulfonyl group.

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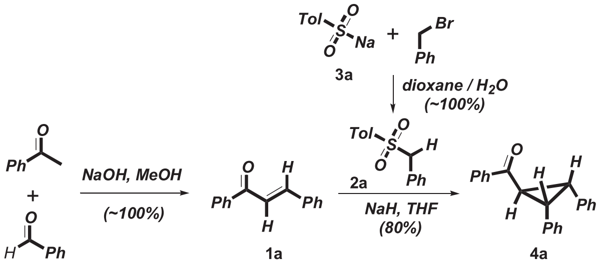
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.02.024



Scheme 1. One-pot route of cyclopropanes **4a**.

To change the bases with different equivalents in various solvents from 25 °C to refluxing temperature, we found different yields of cyclopropane **4a** obtained by the one-pot reaction of model chalcone **1a** with benzyl sulfone **2a** (see Table 1). By adjusting the equivalents of NaH, reaction time, temperature, and concentration (for entries 1–7), the isolated total yield of cyclopropane **4a** was noticeably enhanced (see entry 4). After screening the base-mediated reaction conditions (entries 8–13), we found that NaH provided higher yields than other bases (*t*-BuOK, DBU, DMAP, MeONa). Furthermore, when the base and solvent were replaced with MeONa/MeOH, the isolated total yield of cyclopropane **4a** was decreased to 27% (for entry 13). According to the experimental results, we envisioned that the combination of NaH (4 equiv)/THF (15 mL) is an optimal reaction condition for elevating the total yields of cyclopropane **4a** under boiling THF conditions for 3 h.

Table 1
Reactions of chalcone **1a** and benzyl sulfone **2a**[a]

Entry	Base (equiv), solvent (mL), temp (°C), time (h)	**4a** yield (%)
1	NaH (2.5), THF (15), 25, 3	NR[b]
2	NaH (2.5), THF (15), reflux, 3	52[c]
3	NaH (2.5), THF (15), reflux, 10	72
4	**NaH (4), THF (15), reflux, 3**	**80**
5	NaH (4), THF (15), reflux, 10	75
6	NaH (4), THF (30), reflux, 3	78
7	NaH (10), THF (15), reflux, 3	76
8	*t*-BuOK (4), THF (15), reflux, 3	78
9	*t*-BuOK (4), THF (15), reflux, 10	70
10	*t*-BuOK (10), THF (15), reflux, 3	72
11	DBU (4), THF (15), reflux, 3	45[c]
12	DMAP (4), THF (15), reflux, 3	37[c]
13	MeONa (4), MeOH (15), reflux, 3	27[d]

[a] The reactions were run on a 0.5 mmol scale with chalcone **1a** and benzyl sulfone **2a**.

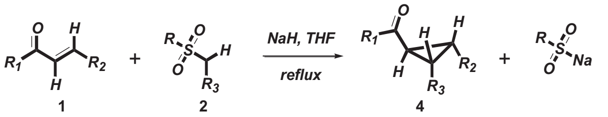
[b] NR is no reaction.

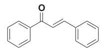
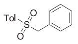
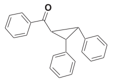
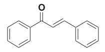
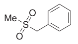
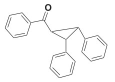
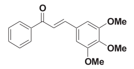
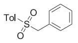
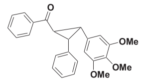
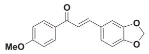
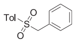
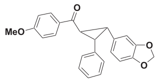
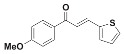
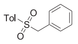
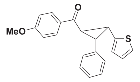
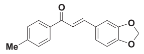
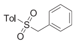
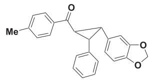
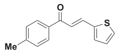
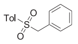
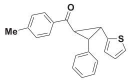
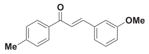
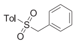
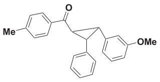
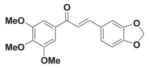
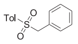
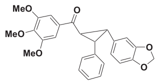
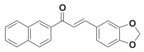
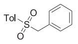
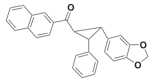
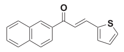
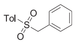
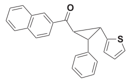
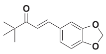
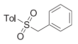
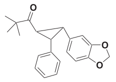
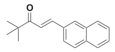
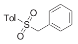
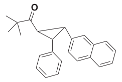
[c] The starting materials **1a** and **2a** were recovery (for entry 2, 25%; entry 11, 38%; entry 12, 45%).

[d] The starting materials **1a** and **2a** (~28%) were recovery and unknown mixture was isolated (~34%).

With the experimental results in hand, one-pot preparation of multisubstituted cyclopropanes **4** was further examined. Changing R_1 and R_2 substituents of chalcones **1a**–**n** and R and R_3 substituents of sulfones **2a**–**h**, 21 cyclopropanes **4a**–**u** with *cis*-diaryl and aroyl groups were isolated with good yields by one-pot methodology (entries 1–22); they are summarized in Table 2. The formation of cyclopropanes **4** was confirmed through spectral analysis, including ^{1}H and ^{13}C NMR and HRMS spectra. The structural frameworks of compounds **4d**, **4l**, **4r**, and **4s** were determined by single-crystal X-ray crystallography, as shown in Fig. 2.[9] But, when the R_3 group was changed to a 4-nitrophenyl or 2,6-difluorophenyl aryl group, a complex unknown mixture was observed (entries 23–24). Alternatively, when the R_1 group was an *n*-octyl or

Table 2
Synthesis of multisubstituted cyclopropanes **4**[a]



Entry	Chalcones **1a**–**x**	Sulfones **2a**–**v**	Cyclopropanes **4a**–**y**/yield (%)
1	 **1a**	 **2a**	 **4a**, 80
2	 **1a**	 **2b**	 **4a**, 72
3	 **1b**	 **2a**	 **4b**, 72
4	 **1c**	 **2a**	 **4c**, 70
5	 **1d**	 **2a**	 **4d**, 70
6	 **1e**	 **2a**	 **4e**, 73
7	 **1f**	 **2a**	 **4f**, 72
8	 **1g**	 **2a**	 **4g**, 78
9	 **1h**	 **2a**	 **4h**, 80
10	 **1i**	 **2a**	 **4i**, 72
11	 **1j**	 **2a**	 **4j**, 70
12	 **1k**	 **2a**	 **4k**, 86
13	 **1l**	 **2a**	 **4l**, 82