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Tandem Knoevenagel−Michael Addition of Aryl Sulfonimines with Diethyl Malonate for Synthesis of Arylidene Dimalonates

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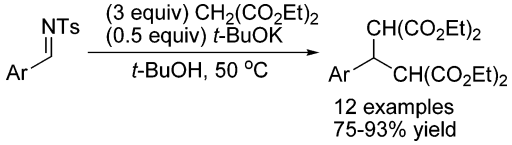
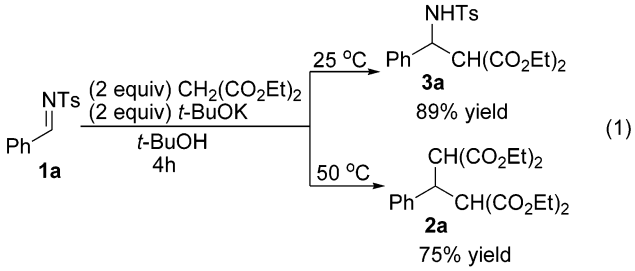


A highly efficient, one-flask tandem Knoevenagel−Michael addition reaction of sulfonimines with diethyl malonate in the presence of a catalytic amount of base affords the corresponding arylidene dimalonates in good to excellent yields.

Arylidene dimalonate has the potential to serve as a bone-affinity agent in the treatment of bone disease,[1] and as the precursor for the synthesis of 3-Ar-glutaric acid.[2] Usually it is synthesized in two steps: the Knoevenagel condensation[3] of aromatic aldehydes with malonate or bromomalonate to form arylidene malonate followed by the Michael addition[4] of arylidene malonate with malonate to produce arylidene dimalonate.[5] Mori has reported a tandem Knoevenagel−Michael addition of alkyl aldehyde with malonate in the presence of stoichiometric piperidinium acetate;[6] however, to our knowledge, no efficient one-flask synthesis of arylidene dimalonate has been reported. On the other hand, sulfonimines are of increasing importance due to their versatility as intermediates in organic synthesis.[7] They are conveniently prepared in various methods,[8] and are employed as electrophiles in a wide variety of addition conditions,[9] which provide a useful route to sulfonamides. We report herein an efficient method for the synthesis of arylidene dimalonates from a one-flask tandem Knoevenagel−Michael addition of aryl sulfonimines with diethyl malonate in the presence of a catalytic amount of base.

Compared to the extensive studies on the nucleophilic addition of sulfonimines, the Mannich-type reaction of sulfonimines with malonates, which can be used to synthesize β-amino acid derivatives,[10] has received much less scrutiny.[11] During the course of our studies on the reactivity of imines,[12] we found that the treatment of sulfonimine **1a** with diethyl malonate at room temperature gave the expected addition product **3a** in 89% yield. However, when the reaction was run at a higher temperature (50 °C), a dual-addition product,[13] benzylidene dimalonate **2a**, was isolated in 75% yield (eq 1). Gong and Kato



(1)

have also observed the dual-addition product in the NaH-induced addition of diethyl malonate to 4-methoxy-*N*-(2,2,2-trifluoro-

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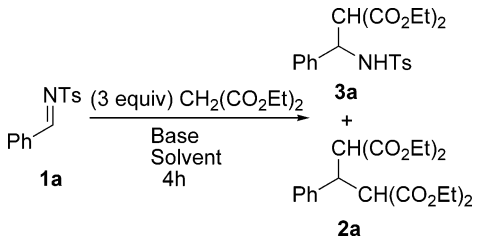
TABLE 1. The Condition Screening Experiments



entry	base (equiv)	solvent	**3a**	**2a**
1	*t*-BuOK (2)	*t*-BuOH	0	89
2	*t*-BuOK (1)	*t*-BuOH	0	88
3	*t*-BuOK (0.5)	*t*-BuOH	0	91
4	*t*-BuOK (0.1)	*t*-BuOH	65	18
5	*t*-BuOK (1)	DMF	10	75
6	*t*-BuOK (1)	DMSO	8	81
7	*t*-BuOK (1)	DCE	15	52
8	*t*-BuOK (1)	H_2O	12	7
9	NaH (1)	*t*-BuOH	10	85
10	K_2CO_3 (1)	*t*-BuOH	16	72
11	Et_3N (1)	*t*-BuOH	56	5

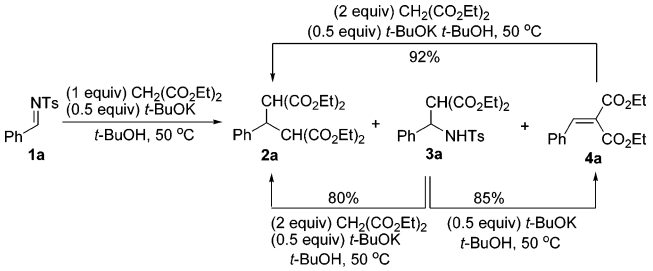
ethylidene)aniline.[14] However, in that case, 1.1 equiv of Lewis acid ($ZnCl_2$) and high temperature (90−110 °C) were required to form the dual-addition product.

As a control experiment, the reaction of benzaldehyde with diethyl malonate under the same condition only gave a trace amount of product **2a** (≤5%). In the following condition screening experiments (Table 1), the yield of **2a** increased to 89% while 3 equiv of ethyl malonate was used. It is noteworthy that a catalytic amount of *t*-BuOK (0.5 equiv) was enough to finish the reaction and to produce **2a** in excellent yield (91%). However, when the amount of *t*-BuOK decreased to 0.1 equiv, the reaction became sluggish and gave **3a** as the major product. *t*-BuOH as solvent and *t*-BuOK as base were proved to be the optimal condition for the tandem reaction, while the combination of other organic solvents and bases gave rise to a mixture of **2a** and **3a**. Although sulfonimines are generally stable, they were hydrolyzed to aldehydes and $TsNH_2$ when the reaction was carried out in water.

When 1 equiv of ethyl malonate was used, the reaction not only gave product **3a** (18% yield) and **2a** (25% yield), but also a benzylidene malonate **4a** in 14% yield. **3a** could not be converted into **2a** by treatment with 1 equiv of ethyl malonate in *t*-BuOH at 50 °C unless 0.5 equivof *t*-BuOK was present in the system. **4a** could also be generated from the reaction of **3a** with *t*-BuOK, and converted into **2a** by the Michael addition with ethyl malonate (Scheme 1).

The above results suggested that the reaction might proceed via a tandem Knoevenagel−Michael addition pathway as shown in Figure 1. The Knoevenagel condensation of sulfonimine **1a** with diethyl malonate was catalyzed by the anion of malonate via an intermediate **A**, which was formed from the Mannich-type reaction. At a lower temperature (25 °C), the elimination reaction of the intermediate **A** could not occur, and then **3a** was obtained as the reaction product. At a higher temperature (50 °C), the Knoevenagel condensation product **4a**, which

SCHEME 1



happens to be an excellent Michael acceptor, was generated from the elimination reaction, and underwent the subsequent Michael addition with the anion of malonate to give the dual-addition intermediate **B**. After a proton exchange with the malonate, benzylidene dimalonate **2a** was formed as the product, and the anion of malonate was regenerated at the same time. During the reaction, **3a** could be observed by TLC, but only trace Knoevenagel product **4a** was detected. So it was supposed that the elimination reaction was the rate-limiting step to the reaction.

The scope of the base-catalyzed tandem Knoevenagel−Michael addition of sulfonimines with diethyl malonate was examined (Table 2). For aryl and heteroaryl sulfonimines, the reactions proceeded smoothly to produce the desirable arylidene dimalonate in good to excellent yields. The presence of an electron-donating group slightly de-

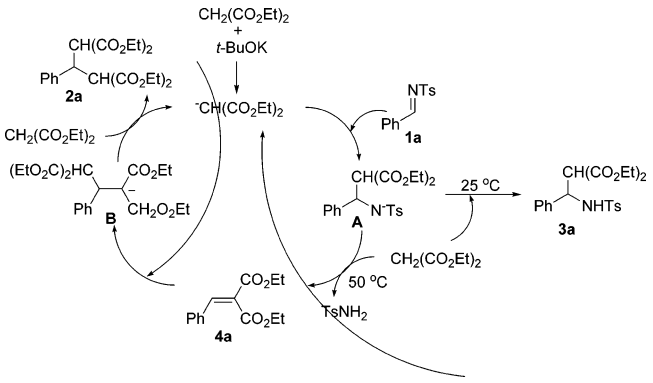
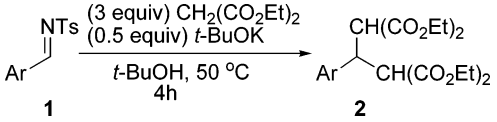


FIGURE 1. A plausible pathway.

TABLE 2. Synthesis of Arylidene Dimalonates



entry	Ar	**2** (%)
1	Ph	**2a** (91)
2	*p*-CH_3O-C_6H_4	**2b** (80)
3	*p*-CH_3-C_6H_4	**2c** (78)
4	*o*,*m*-$(CH_3O)_2$-C_6H_3	**2d** (75)
5	*p*-F-C_6H_4	**2e** (88)
6	*p*-NO_2-C_6H_4	**2f** (92)
7	*p*-I-C_6H_4	**2g** (86)
8	*o*-CF_3-C_6H_4	**2h** (89)
9	*o*-Cl-C_6H_4	**2i** (93)
10	1-naphthyl	**2j** (88)
11	2-furan	**2k** (92)
12	2-thiophen	**2l** (93)

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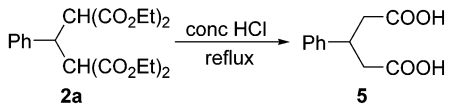
creased its reactivity toward the tandem Knoevenagel−Michael addition. As a consequence, some monoaddition products **3** (≤10% yield) were observed in these cases. The N-substituent of imines played an important role in the reaction. When *N*-phenyl and *N*-benzyl imines were used as the substrates, no expected product was obtained from the reactions.

Decarboxylation of the benzylidene dimalonate **2a** was promoted by heating with hydrochloric acid to give rise to 3-phenylglutaric acid **5** (eq 2).



2a **5** (2)

In summary, we found that arylidene dimalonates could be synthesized in high yields from a one-flask tandem Knoevenagel−Michael addition of sulfonimines with diethyl malonate in the presence of a catalytic amount of *t*-BuOK. A plausible mechanism for this convenient reaction system is presented. The suitable reaction substrates are also tested. Further investigation of the scope, mechanism, and synthetic applications of this reaction is currently underway.

Experiment Section

Typical Procedure for the Tandem Knoevenagel−Michael Addition of Sulfonimines with Diethyl Malonate. A solution of sulfonimine (1 mmol) in anhydrous *t*-BuOH (2 mL) was treated with *t*-BuOK (0.5 mmol). This mixture was stirred at 50 °C under N_2 for 4 h (determined by TLC), then quenched with saturated NH_4Cl, extracted by CH_2Cl_2, and dried by anhydrous Na_2SO_4, and the crude product was purified by flash column chromatography to provide the corresponding product.

Tetraethyl 2-phenylpropane-1,1,3,3-tetracarboxylate (2a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 6H), 1.21 (t, J = 7.3 Hz, 6H), 3.91 (m, 4H), 4.05−4.24 (m, 7H), 7.21 (m, 3H), 7.32 (d, J = 8.8 Hz, 2H). The spectral data are consistent with those reported in the literature.[2a]

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Supporting Information Available: General experimental information, characterization data of the isolated compounds, and ^{1}H and ^{13}C NMR spectra for **2a**−***l***. This material is available free of charge via the Internet at http://pubs.acs.org.

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