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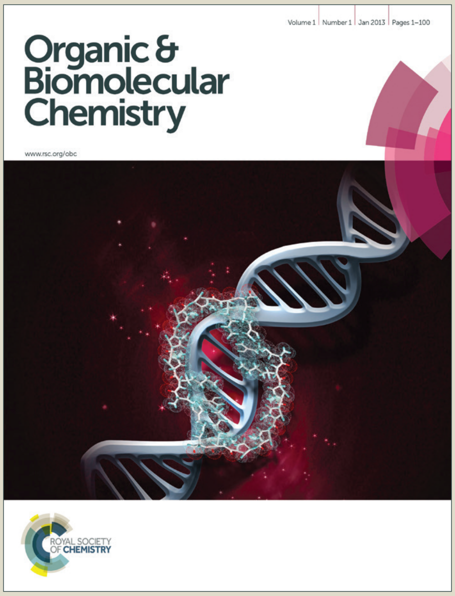

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ARTICLE TYPE

Synthesis of functionalized fulvenes: [3+2] annulation of ethyl α-chlorocyclopropaneformates with 1, 3-dicarbonyl compounds

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A base-promoted [3+2] annulation reaction of ethyl *α*-chlorocyclopropaneformates with 1,3 -dicarbonyl compounds was described. This method provides an efficient straightforward route to acidic multi-substituted fulvenes with distinctive properties in contrast to common fulvenes.

Recently, we found that an electron-deficient cyclopropene **I** is the key intermediate for the fluorination of ethyl *α*-chlorocyclopropaneformates.[1] The unique electron-deficient and highly strained structure would endue **I** with versatile chemical properties. As a continuous work, a mild [3+2] annulation of ethyl *α*-chlorocyclopropaneformates with acetylacetone was observed in our lab, that gave a new type of acidic functionalized fulvenes (Scheme 1, a). This finding demonstrates that **I** is really valuable in organic synthesis and can be used as a new type of synthon with double nucleophilic and electrophilic centers through its C=C bond cleavage as outlined in Fig. 1.

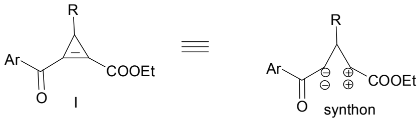
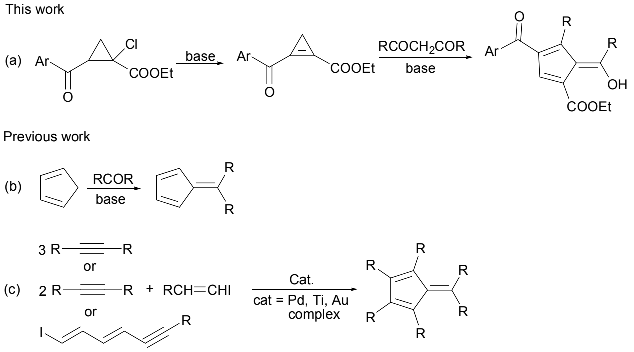


Fig. 1 Synthetic routes of fulvenes

Fulvenes as a kind of important compounds have attracted much attention of chemists involving the study of theoretical arithmetic,[2] the synthesis of natural and bioactive compounds,[3] and the metallocene synthesis.[4] Besides the common base-promoted condensation of cyclopentadiene with carbonyl compounds (Scheme 1, b),[5] the transition-metal-catalyzed coupling reactions of alkynes,[6] and alkynes with vinyl halides,[7] enone or enal moiety[8] also afforded the fulvenes (Scheme 1, c). However, the diversity in structure for the fulvenes reported previously was quite limited. Therefore, we are interested in developing synthetic method of new functionalized fulvenes by utilizing **I** as the synthon. Herein, we described a facile access to 6-hydroxyfulvenes, a kind of antitumor agents,[9] under mild basic conditions.



Scheme 1 Synthetic routes of fulvenes

First, the reaction of substrate **1a** with acetylacetone **2a** was carried out under basic conditions, and the isolated product was identified to be fulvene **3aa** with *Z*-configuration, which was confirmed by single crystal X-ray diffraction analysis (see SI). As shown in Table 1, the properties of both the base and the solvent had a remarkable effect on the reaction. Among all the bases used, Cs_2CO_3 was the most suitable one (Table 1, entry 4). In addition, DMF was the best appropriate in view of the yield of **3aa**. In addition, lowering the reaction temperature from 80 ^{o}C to 50 ^{o}C led to the reaction time prolonged (Table 1, entry 11). The reaction almost did not happen at 25 ^{o}C (Table 1, entry 12).

With the optimized conditions in hand, the scope and limitations of the reaction was next exploited. Thus, a variety of ethyl α-chlorocyclopropaneformates **1a-1j** was tested. The observed results were given in Table 2. Apparently, electronic property of the substituents on benzene ring for **1** had a marked effect on the reaction (Table 2, entries 2-6). Introduction of electron-withdrawing group like Cl or Br could obviously speed up the reaction and elevate the product yields (Table 2, entries 4-6 vs 1-3). Substrates **1g-1i** with 4-biphenyl, 1-naphthyl or 2-thienyl groups were also tolerated for this reaction, giving the products **3ga**, **3ha** and **3ia** in good yields, respectively (Table 2, entries 7-9). In the case of substrate **1j** with a phenyl group at 3-site, the corresponding product **3ja** was also furnished in 61% yield, as well as 12 % yield of its hydrolyzed product (Table 2, entry 10). Decreasing the loading of **2a** to 1.5 equiv. or enlarging the scale 10 times has little effect on the yield (entries 11 and 12).

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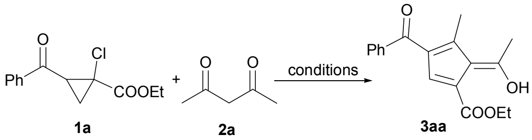
† Electronic Supplementary Information (ESI) available: Experimental procedure, the effect of pH on the ^{1}H NMR of **3aa**, the UV absorption spectra of **8a-8c**, characterization data for compounds, copies of NMR spectra, and X-ray crystallographic data of **3aa** (CIF, CCDC 1019803). See DOI: 10.1039/b000000x/

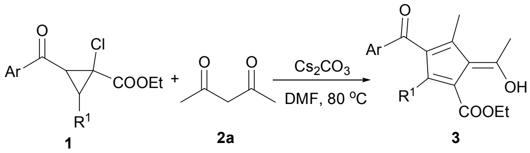
Table 1 Optimization of reaction conditions[a]



entry	base	solvent	temp (°C)	time (h)[b]	conv. (%)	yield (%)[c]
1	t-BuOK	DMF	80	0.8	100	<5
2	KOH	DMF	80	5	90	30
3	K_3PO_4	DMF	80	18	84	55
4	Cs_2CO_3	DMF	80	5	100	67
5	K_2CO_3	DMF	80	12	98	51
6	DBU	DMF	80	0.5	100	7
7	DIPEA	DMF	80	24	0	0
8	Cs_2CO_3	DMSO	80	1	100	<5
9	Cs_2CO_3	CH_3CN	80	12	96	58
10	Cs_2CO_3	THF	66	12	<5	<5
11	Cs_2CO_3	DMF	50	24	100	62
12	Cs_2CO_3	DMF	rt	24	<5	<5

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) and base (0.4 mmol) in solvent (2 mL) was stirred at the specified temperature, then workup with 1M HCl. [b]Determined by TLC. [c]Yields based on converted **1a**.

Table 2 Reaction of **1a-1j** with **2a**[a]



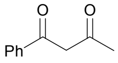
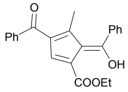
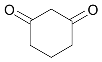
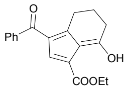
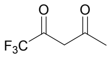
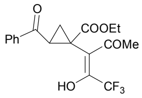
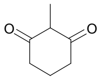
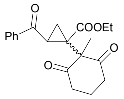
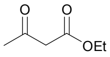
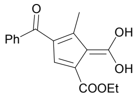
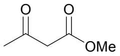
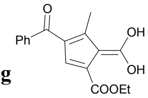
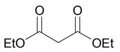
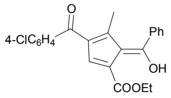
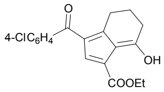
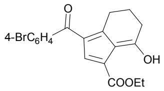
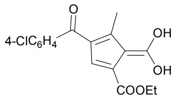
1a: Ar = C_6H_5	R^1 = H	**1f**: Ar = 2-BrC_6H_4	R^1 = H
1b: Ar = 4-MeC_6H_4	R^1 = H	**1g**: Ar = 4-PhC_6H_4	R^1 = H
1c: Ar = 4-$MeOC_6H_4$	R^1 = H	**1h**: Ar = 1-naphthyl	R^1 = H
1d: Ar = 4-ClC_6H_4	R^1 = H	**1i** : Ar = 2-thienyl	R^1 = H
1e: Ar = 4-BrC_6H_4	R^1 = H	**1j**: Ar = C_6H_5	R^1 = C_6H_5

entry	sub 1	time(h)[b]	product	conv. (%)	yield (%)
1	**1a**	5	**3aa**	100	67
2	**1b**	6	**3ba**	100	64
3	**1c**	6	**3ca**	100	63
4	**1d**	1	**3da**	100	87
5	**1e**	1	**3ea**	100	89
6	**1f**	1	**3fa**	100	94
7	**1g**	2	**3ga**	100	71
8	**1h**	5	**3ha**	100	83
9	**1i**	2	**3ia**	100	82
10	**1j**	5	**3ja**	100	61(12[c])
11[d]	**1a**	5	**3aa**	100	66
12[e]	**1a**	6	**3aa**	100	70

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol) and Cs_2CO_3 (0.4 mmol) in DMF (2 mL) was stirred at 80 °C, then workup with 1M HCl. [b]Determined by TLC. [c] the group COOEt was hydrolyzed into COOH . [d]**2a** (0.3 mmol). [e] the scale 10 times enlarged.

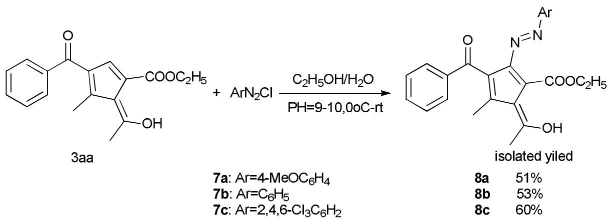
Next, various 1,3-dicarbonyl compounds were also assessed. In the cases of **2b-2h**, the much higher yields were observed when the loading of **2b-2h** changed from 2.0 to 1.5 equivalents. The results were listed in Table 3. With benzoylacetone (**2b**) or cyclohexanedione (**2c**), the reaction of **1a** gave the desired products **3ab** or **3ac** in 67% and 55% yields (Table 3, entries 1-2). With trifluoroacetylacetone (**2d**) or 2-methylcyclohexanedione (**2e**), however, the reaction yielded the formal substitution products **4** or **5** (Table 3, entries 3-4) rather than the expected product. Ethyl acetylacetate (**2f**) and methyl acetylacetate (**2g**) as another typical active methylene compounds were also assessed. A similar product in structure was furnished in the reactions, and characterized to be an unexpected **6a**, a hydrolysis product of the desired compounds with fulvene skeleton by means of ^{1}H and ^{13}C NMR spectroscopy (Table 3, entries 5-6). Diethyl malonate (**2h**) with weaker acidity did not react with **1a** under the same conditions. In addition, electronic property of substituent on benzene ring of **1** had a marked influence on the reaction rate and the product yields (Table 3 entries 8-11).

Table 3 Reaction of **1** with 1,3- dicarbonyl compounds

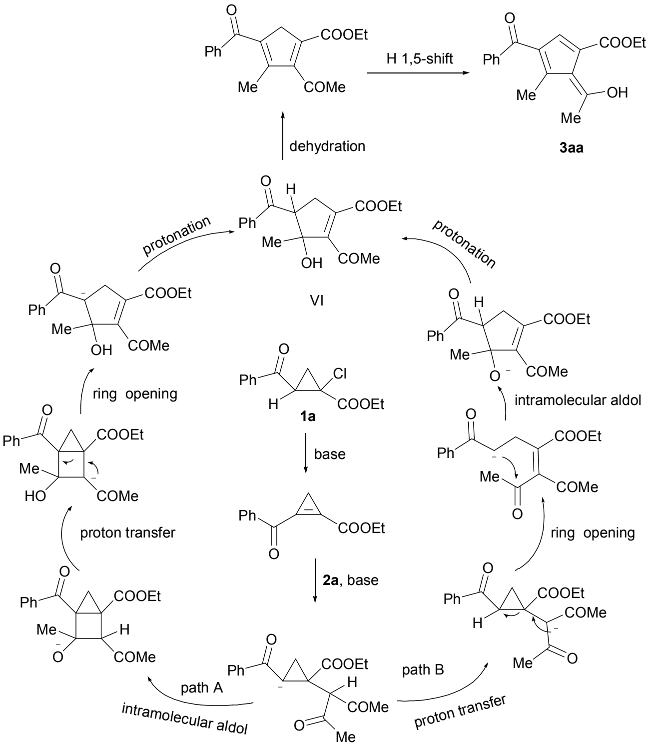
entry	sub **1**	sub **2**	products	yield(%)[a]
1	**1a**	 **2b**	 **3ab** (6 h)	67
2	**1a**	 **2c**	 **3ac** (2 h)	55
3	**1a**	 **2d**	 **4** (6 h)	56
4	**1a**	 **2e**	 **5** (1 h)	49
5	**1a**	 **2f**	 **6a** (5 h)	62
6	**1a**	 **2g**	 **6a** (6 h)	75
7	**1a**	 **2h**	None	/
8	**1d**	**2b**	 **3db** (1.5 h)	80
9	**1d**	**2c**	 **3dc** (0.5 h)	64
10	**1e**	**2c**	 **3ec** (0.5 h)	93
11	**1d**	**2f**	 **6d** (2 h)	79

[a] isolated yields, the conversion for each case is 100%.

The effect of carbonyl groups on the acidity of products **3** was assessed by means of spectroscopic analysis (see SI). In fact, only simple proton transfer reaction rather than reduction took place when **3aa** was treated with $NaBH_4$ in methanol. For this reason, the reactivity of **3aa** was evaluated by performing its reaction with diazo salt **7a-7c** in weak alkaline solution. As depicted in Scheme 2, three new azo compounds **8a-8c** were afforded in good yields. All the above results clearly indicate that compound **3aa** exists in its anion form under alkalescent conditions. Additionally, it should be noted that the characteristic absorption of visible lights for **8a**, **8b** and **8c** denoted they could be used as a new kind of azo dye.



Scheme 2 The diazotization reaction of **3aa** with diazonium salts



Scheme 3 Proposed mechanism

A possible mechanistic explanation was also proposed to rationalize the formation of **3aa** as outlined in Scheme 3. The key steps involve the generation of cyclopropene intermediate I via 1,2-elimination of **1a**, nucleophilic addition of I with carbanion to adduct II, and subsequent transformation of II. Conversion of the adduct II to five-membered intermediate III would undergo along with path A or path B, though the details still kept unclear. The fulvene **3aa** was finally yielded through fast dehydration of III driven by the formation of conjugated system and complete enolization. The intramolecular hydrogen-bonding between hydroxyl and ethoxycarbonyl groups of **3aa** led to the preferential formation of its Z-isomer.

Conclusions

In summary, we have developed an unprecedented efficient route to access a variety of functionalized 6-hydroxylfulvenes bearing two carbonyl groups. To the best of our knowledge, this is first example for the synthesis of 6-hydroxyl-acylfulvene that possess unique properties via cyclopropene intermediate generated in situ. Further work aimed at exploring their chemical behavior and applications are underway currently in our laboratory.

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