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Acid-promoted $S_N1/E1$ fragmentation/dimerization of 2-cumylmalonates

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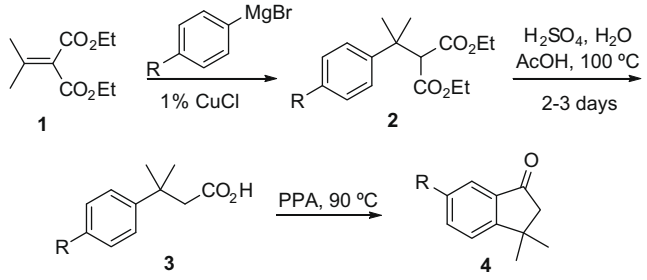
ABSTRACT

Several diethyl 2-cumylmalonates underwent fragmentation and dimerization in PPA at elevated temperatures to give 1,1,3-trimethyl-3-arylindanes in good yields. The same products were obtained from 2-cumylmalonic acid, ethyl 2-cumylcyanoacetate, and 2-cumyl Meldrum's acid. This represents the first example of an $S_N1/E1$ ionization with diethyl malonate as the leaving group.

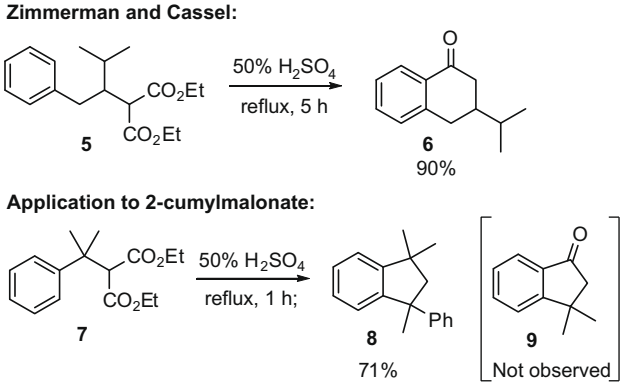
1. Introduction

Recently we required an efficient and scalable synthesis of 4- and 6-substituted 3,3-dimethyl-1-indanones. The most attractive approach, involving Friedel–Crafts reaction of arenes with 3,3-dimethylacrylic acid followed by intramolecular cyclization, suffered from poor regioselectivity in the Friedel–Crafts reaction.[1] A regiospecific approach (Scheme 1) was identified starting from isopropylidene malonate **1**.[2] Copper chloride-catalyzed conjugate addition of aryl Grignard reagents with **1** gave the adducts **2**.[3] Hydrolysis/decarboxylation of **2** gave the acids **3**, which were cyclized in PPA to give the desired indanones **4**.[4]



Scheme 1. Regiospecific synthesis of 3,3-dimethyl-1-indanones.

While the above three-step route was scalable and provided the target indanones in good yields, the long reaction time required for the hydrolysis/decarboxylation was undesirable. Zimmerman and Cassel reported the direct conversion of malonate **5** to tetralone **6** in refluxing 50% H_2SO_4 (Scheme 2).[5] This precedent suggested that the direct conversion of malonates **2** to indanones **3** may be possible, using more strongly acidic conditions to effect hydrolysis/decarboxylation/intramolecular cyclization in a single pot. Intrigued by the possibilities of shortening our indanone synthesis from three steps to two steps, and reducing cycle time, we applied the Zimmerman conditions to 2-cumylmalonate **7**. The starting material was quickly converted under these conditions to a highly nonpolar product which was isolated and identified as indane **8**. None of the desired indanone **9** was detected in the reaction mix-



Scheme 2. Zimmerman's tetralone synthesis and application to our system.

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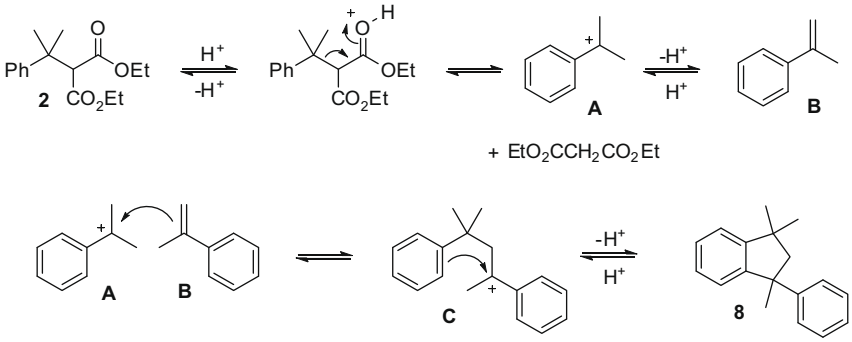


Scheme 3. Proposed mechanism for indane formation.

ture. Subsequently it was found that the reaction occurred in higher yield using PPA (polyphosphoric acid) at 90 °C (83% yield). The reaction also occurred in concentrated H_2SO_4 (20 °C, 10 min), though some ring-sulfonylation also took place.

Our proposed mechanism for formation of **8** is shown in Scheme 3. Initial protonation of **2** is followed by C–C bond ionization to give cumyl cation **A** and diethyl malonate. Cation **A** may undergo proton loss to give α-methyl styrene **B** (E1 reaction). Attack of **B** onto **A** (S_N1 reaction for **A**) gives intermediate **C**, which cyclizes to indane **8**. The formation of 1,1,3-trimethyl-3-arylindanes from α-methylstyrenes under Bronsted or Lewis acid catalysis is known.[6] The thermal ionization of *tert*-butyl- and cumyl-tricyanomethanes and dicyanonitromethanes has been studied by Mitsuhashi and co-workers.[7] To the best of our knowledge, the present case represents the first report of diethyl malonate acting as a leaving group in an S_N1 or E1 reaction.[8–11] The reaction is also a unique pathway to substituted 1,1,3-trimethyl-3-arylindanes.

The scope of the reaction was examined with several substituted 2-cumylmalonates (Table 1). *Para*-substituted (entries 2–5), *ortho*-substituted (entry 6), and 1-naphthyl (entry 7) substrates

Table 1
Ionization/dimerization of 2-cumylmalonates with PPA[a]

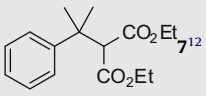
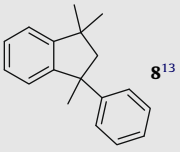
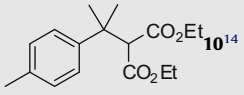
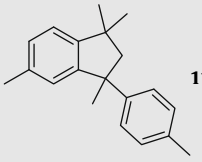
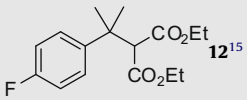
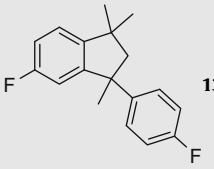
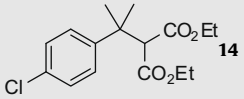
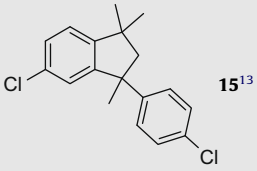
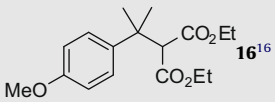
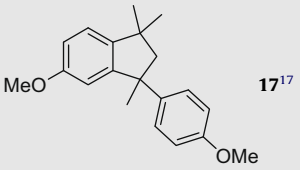
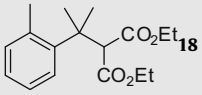
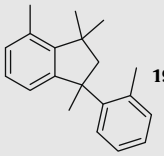
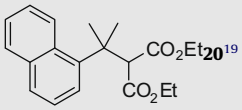
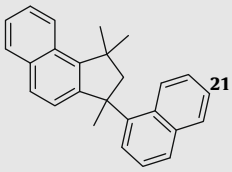
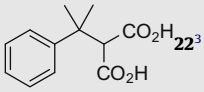
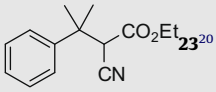
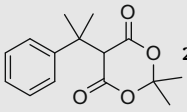
Entry	1,4-Adduct	Indane	Time	Yield[b]
1	 **7**[12]	 **8**[13]	1	83
2	 **10**[14]	 **11**[13]	3	85
3	 **12**[15]	 **13**	1	75
4	 **14**	 **15**[13]	20	70
5	 **16**[16]	 **17**[17]	1	82

Table 1 (*continued*)

Entry	1,4-Adduct	Indane	Time	Yield[b]
6	 **18**	 **19**[18]	0.5	74
7	 **20**[19]	 **21**	0.5	73
8	 **22**[3]	**8**	1	80
9	 **23**[20]	**8**	2	78
10	 **24**[21]	**8**	2	52[c]

[a] Reaction conditions: To PPA preheated to 90 °C was added substrate (neat).
[b] Isolated yield after chromatography on SiO_2.
[c] 3-Methyl-3-phenylbutyric acid was also isolated in 26% yield.

all gave the indane products in good yields. Interestingly, the *para*-chloro substrate **14** reacted unusually slowly, though the product indane **15** was nonetheless obtained in good yield. The success of the reaction is not limited to diethyl malonate as leaving group (entries 8–10). 2-Cumyl-substituted malonic acid, cyano ester, and Meldrum's acid systems also gave the indane in good yields. Notably, the reaction of Meldrum's acid-derived substrate **24** gave a significant amount of 3-methyl-3-phenylbutyric acid in addition to indane **8**, indicating that the normal decomposition path of the Meldrum's acid moiety was competitive with the ionization/dimerization reaction.

In conclusion, we have described the unexpected conversion of 2-cumylmalonates to 1,1,3-trimethyl-3-arylindanes on exposure to strongly acidic conditions. The indane products can be formed in the highest yields using PPA at 90 °C. This work represents the first example of diethyl malonate acting as a leaving group in an S_N1/E1 reaction. This work also demonstrates that the strength of acidic conditions must be carefully chosen when hydrolyzing/decarboxylating 2-cumylmalonic acid esters and related systems.

2. Experimental

2.1. General

Conjugate addition products were prepared according to the general procedure described below, with the exception of **22**, which was prepared according to Ref. 3. 1,1,3-Trimethyl-3-arylindanes were prepared according to the general procedure described below. Literature references for all known compounds are given in Table 1, and spectral data for these compounds were in agreement with the published data. Data for new compounds **13, 14**, **18**, and **21** are given below.

2.2. General procedure for aryl Grignard addition to 1.[3] Diethyl 2-(2-(4-chlorophenyl)propan-2-yl)malonate (14)

A flask was charged with CuCl (50.5 mg, 0.51 mmol, 0.01 equiv) and 4-chlorophenylmagnesium bromide (53.5 mL, 53.5 mmol, 1.0 M/THF, 1.05 equiv). The mixture was cooled to 0 °C and was treated dropwise with diethyl isopropylidene malonate **1** (10.0 mL, 51.0 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min at 0–10 °C, at which time HPLC analysis indicated consumption of **1**. The reaction mixture was quenched with 6 N HCl (50 mL), 50 mL of hexanes was added, and the layers were separated. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by chromatography on silica gel (hexanes/EtOAc 9:1) to give **14** as a colorless oil, 12.6 g, 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 2H, J = 8.3 Hz), 7.25 (d, 2H, J = 8.3 Hz), 4.10–4.00 (m, 4H), 3.76 (s, 1H), 1.58 (s, 6H), 1.15–1.06 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 144.5, 131.0, 127.0, 126.5, 60.6, 59.9, 38.7, 25.2, 12.8; Anal. Calcd for $C_{16}H_{21}O_4Cl$: C, 61.44; H, 6.77. Found: C, 61.51; H, 6.80.

2.3. Diethyl 2-(2-*o*-tolylpropan-2-yl)malonate (18)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.35 (m, 1H), 7.14–7.06 (m, 3H), 4.25 (s, 1H), 4.06–3.95 (m, 4H), 2.57 (s, 3H), 1.66 (s, 6H), 1.11–1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

168.1, 144.2, 135.7, 132.9, 127.4, 126.6, 125.7, 60.8. 58.5, 41.2, 26.8, 23.3, 13.8; Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.71; H, 8.40.

2.4. General procedure for 1,1,3-trimethyl-3-arylindane formation. 5-Fluoro-3-(4-fluorophenyl)-1,1,3-trimethylindane (13)

A flask was charged with PPA (10.0 mL) and heated to 90 °C with stirring. Compound **12** (1.0 g) was charged neat dropwise (solid compounds were added portionwise). The reaction mixture was held at 90 °C for the time listed in Table 1 (until consumption of starting material as determined by HPLC analysis). The reaction mixture was cooled to 30–40 °C, quenched with water (70 mL), and stirred until all PPA was hydrolyzed. EtOAc was added and the layers were separated. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by chromatography on silica gel (hexanes) to give **13** as a white solid, 345 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.08 (m, 3 H), 6.99–6.88 (m, 3 H), 6.78–6.73 (m, 1H), 2.38 (d, 1H, J = 12.8 Hz), 2.21 (d, 1H, J = 12.8 Hz), 1.65 (s, 3H), 1.32 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 162.2, 161.1, 159.8, 150.8, 147.6, 146.0, 128.1, 128.0, 123.8, 123.7, 114.8, 114.6, 114.55, 114.3, 111.5, 111.3, 59.6, 50.2, 42.4, 30.8, 30.75, 30.5; Anal. Calcd for $C_{18}H_{18}F_2$: C, 79.39; H, 6.66. Found: C, 79.20; H, 6.82.

2.5. 1,1,3-Trimethyl-3-(naphthalen-1-yl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene (21)

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.45 (m, 8H), 7.26–7.05 (m, 3 H), 6.94–6.74 (m, 2H), 3.04 (d, 1H, J = 16 Hz), 2.01 (s, 3H), 2.00–1.90 (m, 1H), 1.61 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 144.6, 143.7, 135.3, 134.3, 130.5, 129.2, 128.1, 127.5, 126.5, 126.1, 125.7, 124.9, 124.6, 124.5, 122.8, 59.3, 50.8, 44.1, 35.0, 34.6, 33.9; Anal. Calcd for $C_{26}H_{24}$: C, 92.81; H, 7.19. Found: C, 92.74; H, 7.29.

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