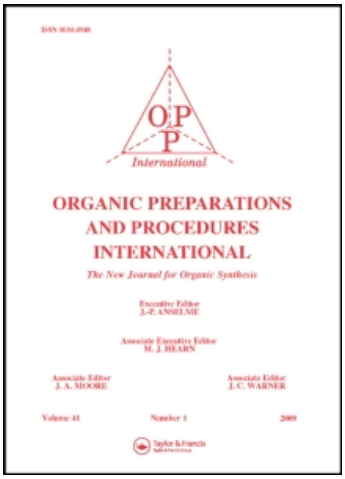

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CONVENIENT SYNTHESIS OF 1-ACETYL-2,2-DIMETHYL-3-ARYLCYCLOPROPANES

Submitted by Lakshmi Muthusubramanian*† and Rajat B. Mitra††
(07/06/07)

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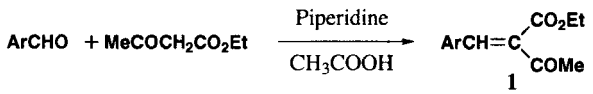
Synthetic pyrethroids are derived from natural pyrethrin and have been extensively exploited commercially as insecticides on various crops and as pest control agents in household applications. Many powerful pyrethyroid insecticides possess a relatively low acaricidal action. However, pyrethyroids bearing a 3-aryl substituent in the 2,2-dimethylcyclopropanecarboxylic acid moiety have recently displayed strong acaricidal activity.[1,2] They are generally prepared from diazoacetic esters[3] which are not only hazardous in scale-up but also pose a serious toxicological problem when prepared from nitrosamides. Although these systems have their own merits, they also have drawbacks such as high temperatures, expensive catalysts and tedious operation. We now report an efficient three-step procedure which gives 1-acetyl-2,2-dimethyl-3-arylcyclopropanes (**5**), from the Michael initiated ring closure (MIRC) reaction of potassium 2-nitropropane on the cinnamates (**1**) followed by de-ethoxycarbonylation in 35-80% overall yields.

The strategy involves the use of the acetyl group to activate the electrophilic olefinic precursors for the cyclopropanation reaction with potassium 2-nitropropane. Knoevenagel condensation of substituted benzaldehydes with ethyl acetoacetate furnished ethyl 2-acetylcinnamates (**1**) with the acetyl group *trans* to the aryl. The addition of nitroalkane anions to electron-deficient olefins (Michael reaction) has been used extensively in organic synthesis,[4,5] including



1

a) Ar = C_6H_5, b) Ar = *p*-ClC_6H_4, c) Ar = *p*-$CH_3OC_6H_4$

reports of cyclopropane formation.[6,7] The fact that the stereochemistry of cinnamates was retained in the course of the reaction indicates that the reaction proceeds *via* intermediates similar to those of the Knoevenagel reaction.[8] The tertiary nitro group is particularly prone to intramolecular displacement to give cyclopropanes. This fact strongly suggests that the present ring closure proceeds *via* single electron-transfer as in other reactions of nitro compounds with nucleophiles.

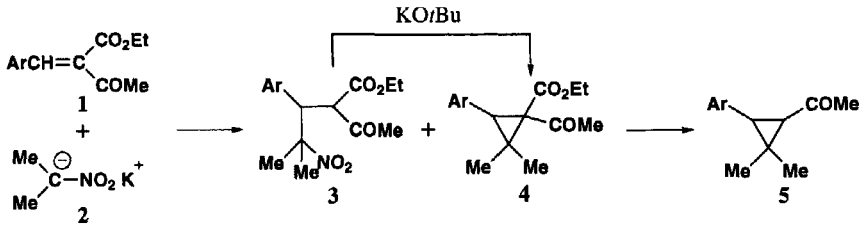


Table 1. Yield, mps, IR and NMR Spectral Data

Cmpd	Yield (%)	mp (°C)	IR (cm^{-1})	^1H NMR (δ)	MS m/z (M^+)
1a	75	78-80	1360, 1600, 1750 (C=O), 2860, 3000	1.26 (t, 3H, J = 7.2 Hz), 2.41 (s, 3H), 4.28 (q, 2H, J = 7.2Hz), 7.39 – 7.55 (m, 6H)	218
1b	40	84-86	790, 1370, 1740 (C=O), 2850, 2900	1.24 (t, 3H, J = 7.2 Hz), 2.43 (s, 3H), 4.29 (q, 2H, J = 7.2 Hz), 7.35 – 7.45 (m, 5H)	252
1c	50	90-92	800, 1360, 1720 (C=O), 2820, 2860, 3000	1.22 (t, 3H, J = 7.2 Hz), 2.43 (s, 3H), 3.70 (s, 3H), 4.25 (q, 2H, J = 7.2 Hz), 7.34 – 7.44 (m, 5H)	248
3a	35	100-102	1360, 1380, 1600, 1750 (C=O), 2860, 3000	1.28 (s, 3H), 1.34 (t, 3H), J = 7.2 Hz), 2.42 (s, 3H), 1.62 (s, 3H), 4.28 (q, 2H, 7.2 Hz), 4.37 – 4.87 (AB, d, 2H = 11.7 Hz), 6.97 – 7.60 (m, 5H)	307
3b	50	107-109	790, 1360, 1380, 1750 (C=O), 2850, 3000	1.32 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz), 1.62 (s, 3H), 2.43 (s, 3H), 4.28 (q, 2H, J = 7.2 Hz), 4.36 – 4.82 (AB, d, 2H, J = 11.7 Hz), 6.97 – 7.60 (m, 4H)	341
3c	60	113-115	800, 1350, 1380, 1750 (C=O), 2860, 3000	1.30 (s, 3H), 1.34 (t, 3H, J = 7.2 Hz), 1.60 (s, 3H), 2.42 (s, 3H), 3.76 (s, 3H), 4.28 (q, 2H, J = 7.2 Hz), 4.35 – 4.80 (AB, d, 2H, J = 11.7 Hz), 6.96 – 7.51 (m, 4H)	337
4a	35	97-99	1360, 1380, 1610, 1750 (C=O), 2850, 3000, 3050	0.93 (t, 3H, J = 7.2 Hz), 1.22 (s, 3H), 1.70 (s, 3H), 2.42 (s, 3H), 3.65 (s, 1H), 4.21 (q, 2H, J = 7.2 Hz), 7.37 – 7.51 (m, 5H)	260
4b	40	104-106	1350, 1380, 1750 (C=O), 2860, 3000, 3050	0.96 (t, 3H, J = 7.2 Hz) 1.21 (s, 3H), 1.67 (s, 3H), 2.45 (s, 3H), 3.62 (s, 1H), 4.23 (q, 2H, 7.2 Hz), 7.38 – 7.56 (m, 4H)	295
4c	45	109-111	790, 1350, 1380, 1750 (C=O), 2860, 3000, 3050	0.95 (t, 3H, 7.2 Hz), 1.21 (s, 3H), 1.75 (s, 3H), 2.47 (s, 3H), 3.62 (s, 1H), 3.72 (s, 3H), 4.22 (q, 2H, 7.2 Hz), 7.35 – 7.52 (m, 4H)	290

Table 1. Continued...

Cmpd	Yield (%)	mp (°C)	IR (cm^{-1})	^1H NMR (δ)	MS m/z (M^+)
5a	60	Viscous colorless oil	1360, 1380, 1600, 3050	*trans*-isomer: 0.93 (s, 3H), 1.37 (s, 3H), 1.98 (d, 1H, J = 6.3 Hz), 2.42 (s, 3H), 2.71 (d, 1H, J = 6.3 Hz), 7.20 – 7.29 (m, 5H), *cis*-isomer: 1.32 (s, 3H), 1.36 (s, 3H), 1.87 (d, 1H, J = 9.2 Hz), 2.43 (s, 3H), 2.47 (d, 1H, J = 9.2 Hz), 7.20 – 7.28 (m, 5H)	188
5b	75	Viscous colorless oil	800, 1360, 1380, 1600, 3000, 3050	*trans*-isomer: 0.92 (s, 3H), 1.37 (s, 3H), 1.92 (d, 1H, J = 5.8 Hz), 2.41 (s, 3H), 2.65 (d, 1H, J = 5.8 Hz) 7.03 – 7.31 (m, 4H). *cis*-isomer: 1.30 (s, 3H), 1.35 (s, 3H), 1.87 (d, 1H, J = 9.00 Hz), 2.38 (d, 1H, J = 9.00 Hz), 2.42 (s, 3H), 7.03 – 7.31 (m, 4H)	223
5c	80	Viscous colorless oil	820, 1360, 1380, 1600, 3000	*trans*-isomer: 0.92 (s, 3H), 1.33 (s, 3H), 1.86 (d, 1H, J = 6.3 Hz), 2.42 (s, 3H), 2.66 (d, 1H, J = 6.3 Hz), 3.76 (s, 3H), 6.78 – 7.26 (m, 4H), *cis*-isomer: 1.24 (s, 3H), 1.29 (s, 3H), 1.75 (d, 1H, J = 9 Hz), 2.42 (s, 3H), 3.76 (s, 3H), 2.58 (d, 1H, J = 9 Hz), 6.78 – 7.26 (m, 4H)	218

Table 2. Elemental Analysis of Compounds **1**, **3**, **4** and **5**

Cmpd	Calcd % (Found)		
	C	H	N
1a	71.56 (71.59)	6.42 (6.48)	----
1b	61.90 (61.92)	5.15 (5.20)	----
1c	67.74 (67.70)	6.45 (6.49)	----
3a	62.54 (62.61)	6.84 (6.88)	4.56 (4.60)
3b	56.30 (56.27)	5.86 (5.82)	4.10 (4.08)
3c	60.53 (60.56)	6.82 (6.86)	4.15 (4.18)
4a	73.84 (73.97)	7.69 (7.84)	----
4b	65.08 (65.20)	6.44 (6.60)	----
4c	70.34 (70.19)	7.58 (7.41)	----
5a	82.97 (83.18)	8.51 (8.76)	----
5b	69.95 (70.16)	6.72 (6.95)	----
5c	77.06 (77.00)	8.25 (8.18)	----

Compounds **3a-c** where *erythro*/*threo* isomerism is possible, appeared to be mainly one diastereomers (50-75% yield)[9] accompanied by lesser quantities of **4** (35-45% yields)[9] and possibly the other diastereomers. Treatment of crude **3a-c** with equimolar amount of potassium *t*-butoxide converted **3a-c** into **4a-c** in 35-45% yield. Thus, the total yield of **4a-c** from **1a-c** range from 70-

80%. Recrystallization of **4a-c** from ethanol gave the pure diastereomers as shown by their NMR spectrum which showed sharp singlets at ~ δ 3.62-3.65 for the cyclopropyl protons and two sharp 3H signals at ~ δ 1.21-1.22 and 1.67-1.75 for the two *gem*-dimethyl groups. De-ethoxycarbonylation of **4** with potassium hydroxide in ethylene glycol at 170°C for 2 h, afforded 1-acetyl-2,2-dimethyl-3-arylcyclopropane (**5a-c**) as 35:65 mixtures of *cis/trans* isomers as evidenced by chemical shifts of the *gem*-dimethyl groups and coupling constants of the cyclopropyl protons in the ^{1}H NMR spectrum. The stereochemical assignments were based on the known coupling constants (9-10 Hz) for *cis*-vicinal cyclopropyl hydrogens which are greater than those of the *trans*-isomer (6-7 Hz) and the greater chemical shift difference for the geminal CH_3 of the *trans*-isomer. These values were in agreement with those reported.[10,11] The isomer composition of **5** appears to be the result of a thermodynamic control operating during its formation. Commercial pyrethroids such as permethrin and cypermethrin have similar equilibrium compositions of *cis/trans* isomers.[12] The overall yields of **5** from ethyl acetoacetate in the three steps was around 50% without any optimization. The simplicity and ease of these operations using inexpensive commercial chemicals make this synthetic procedure viable in a large-scale manufacturing process.

EXPERIMENTAL SECTION

IR spectra were obtained on Nicolet 20 DXB FT-IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ with a Brucker CXP-90 MHz pulse spectrometer using TMS as internal standard. Mass spectra were acquired on a HP 5890 series II gas chromatograph with a 5971 as a mass selective detector. Column chromatography was performed on silica gel (Merck 60-120 mesh). Silica gel precoated plates with fluorescent indicator were used for thin layer chromatography. Developed plates were visualized by UV light and petroleum ether (60-80°C) was used as an eluent. *Ethyl 2-Acetylcinnamates* (**1a-c**) were obtained as white powders according to the reported procedure.[13]

***Ethyl 2-Acetyl-3-aryl-4-nitro-4-methylpentanoate* (3a-c) *and Ethyl 2,2-Dimethyl-1-acetyl-3-arylcyclopropanecarboxylate* (4a-c). *General Procedure*.-** A mixture of the potassium salt of 2-nitropropane[12] (2.54 g, 20 mmol), prepared by addition of 2-nitropropane to potassium *t*-butoxide, and compounds **1a-c** (1 mmol) in dimethyl sulfoxide (10 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with water, extracted with methylene chloride and the organic layer washed with water and dried over sodium sulfate. The organic layer was concentrated under reduced pressure to give a crude oily residue. The crude compound was subjected to column chromatography on silica gel using ethyl acetate/petroleum ether (20:80) to afford **3a-c** as white powders and **4a-c** as pale yellow powders. Treatment of compounds **3a-c**, contaminated with a small amount of **4a-c** and possibly the other diastereomer, with an equimolar amount of KO*t*Bu in DMSO, gave **4a-c** in 50-60% yield. Thus, with the recycling of **3a-c**, the total yield of **4a-c** ranged from 60-80%.

***1-Acetyl-2,2-dimethyl-3-arylcyclopropane* (5a-c). *General Procedure*.-** A stirred mixture of **4a-c** (1 mmol) and potassium hydroxide (3 mmol) in ethylene glycol (10 mL) was heated at 170–172°C for 4 h. The resulting mixture was poured into a saturated aqueous sodium chloride. Extraction with chloroform was followed by washing with water and drying over sodium sulfate. The organic solvent was removed under reduced pressure and the residue subjected to column chromatography on silica gel using ethyl acetate/petroleum ether (25:75) to give **5a-c** in 60-80% yield.

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