Synthesis and Structures of 6-Aryl-1,5-dimethoxycarbonyl-2-methyl-4-morpholino-1,3-cyclohexadienes and Related Compounds

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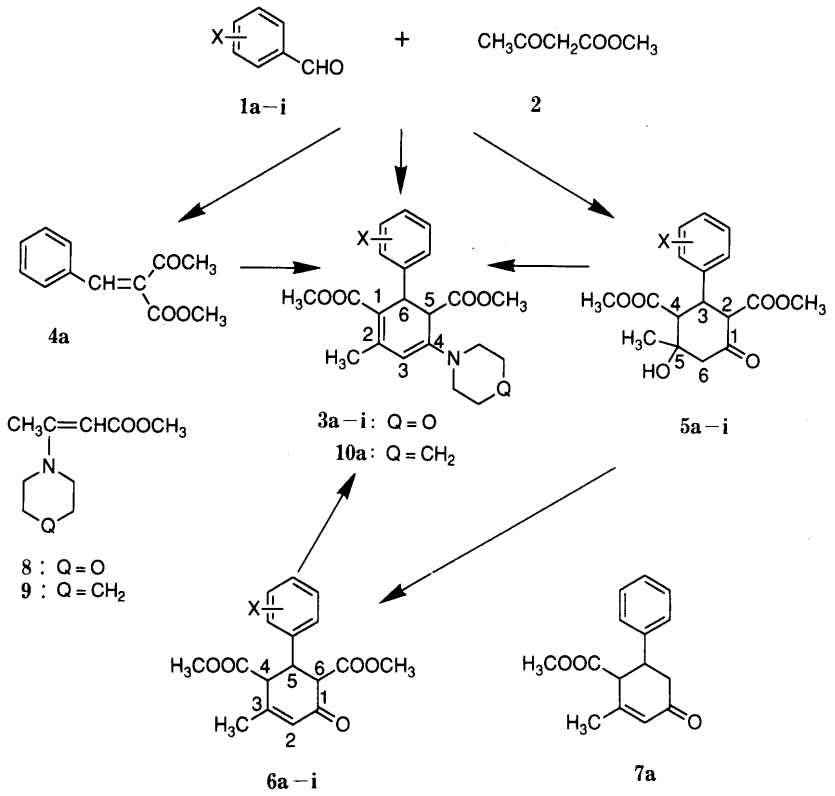
Reaction of benzaldehyde (1a) with methyl acetoacetate (2) in the presence of morpholine (or piperidine) and AcOH in refluxing C_6H_6 yielded a new condensation product, 1,5-dimethoxycarbonyl-2-methyl-4-morpholino (or piperidino)-6-phenyl-1,3-cyclohexadiene (3a or 10a), along with a usual product, benzylideneacetoacetate (4a). Under the conditions determined as optimum, 3a was prepared in 86% yield. However, reaction of 1a and 2 in the presence of morpholine (or piperidine) in EtOH solution yielded 4a, a poly-substituted cyclohexanone derivative (5a) and a cyclohexenone derivative (7a), while the production of 3a was not detected. Compound 3a (or 10a) was also prepared by an alternative procedure of condensation of 5a or 6a with morpholine (or piperidine) in the presence of $TiCl_4$. Compound 6a was prepared by dehydration of 5a under acidic conditions. Acid hydrolysis of 3a afforded 6'a, which is the C-4 epimer of 6a. The configurations of 3a, 6a and 6'a were assigned on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra. Mechanisms of the formation of 3a are discussed. Some of 3 and related compounds exhibited potent calcium channel-blocking activity.

Keywords Knoevenagel reaction; cyclohexadiene, poly-substituted; 6-aryl-1,5-dimethoxycarbonyl-2-methyl-4-morpholino-1,3-cyclohexadiene; enamine; calcium channel-blocking activity

The Knoevenagel reaction of an aldehyde with acetoacetic acid esters, in a molar ratio of one to two, in the presence of a catalytic amount of primary and secondary amines leads to alkylideneacetoacetic acid esters, $RCH=C(COCH_3)COOR$[1]; The procedure is simple and isolation of the product is generally straightforward.[1] However, many condensations have led to unexpected products through of secondary reactions such as Michael and Dieckmann condensations.[1] This paper describes the synthesis and structures of new condensation products, 6-aryl-1,5-dimethoxycarbonyl-2-methyl-4-morpholino-1,3-cyclohexadienes (3) and related compounds, of which some exhibited significant calcium channel-blocking activity.[2]

Results and Discussion

The reactions are outlined in Chart 1. Reaction of benzaldehyde (**1a**) with methyl acetoacetate (**2**) in the presence of catalytic amounts of morpholine and AcOH in



X : **a** = H, **b** = *o*-NO_2, **c** = *m*-NO_2, **d** = *p*-NO_2, **e** = *m*-OCH_3, **f** = *p*-OCH_3, **g** = *m*-CH_3, **h** = *p*-CH_3, **i** = *m*-Cl

Chart 1

TABLE I. Reaction of Benzaldehyde (**1a**) with Methyl Acetoacetate (**2**) in the Presence of Morpholine and AcOH[a]

Entry No.	Equimolecular amount of Morpholine	AcOH	Products Yield[b] (%) 3a	4a
1	0.1	0.1	nd	85
2	0.25	0.25	6	75
3	0.5	0.5	47	48
4	1.0	0.5	80	nd
5	1.5	0.5	86	nd

a) A mixture of **1a** and 2 molar eq of **2** was run in the presence of morpholine and AcOH in the amounts described in the table in refluxing C_6H_6 for 18 h. *b*) Isolated yield. nd: not detected.

refluxing C_6H_6 gave 1,5-dimethoxycarbonyl-2-methyl-4-morpholino-6-phenyl-1,3-cyclohexadiene (**3a**) along with methyl benzylideneacetoacetate (**4a**)[3-5] as a main product (no attempt was made to isolate other products). As can be seen in Table I, an increase in amount of morpholine led to an increased yield of **3a**. When a mixture of **1a** and 2 molar eq of **2** was treated with 0.1 molar eq each of morpholine and AcOH, only **4a** was isolated in 85% yield (entry No. 1). As shown in entries 2, 3 and 4, **3a** was produced in increasing yields as the molar ratio of morpholine was increased. The reaction with morpholine and AcOH at 0.5 molar eq each (entry No. 3) gave **3a** and **4a** in 47% and 48% yields, respectively. The optimum condition for the preparation of **3a** involved the reaction of a mixture of **1a** and 2 molar eq of **2**, 1.5 molar eq of morpholine and 0.5 molar eq of AcOH for 18 h in refluxing C_6H_6, the water produced being removed azeotropically. When reaction of **1a** and **2** was run in the presence of piperidine and AcOH for 8 h in refluxing C_6H_6, 1,5-dimethoxycarbonyl-2-methyl-6-phenyl-4-piperidino-1,3-cyclohexadiene (**10a**) was obtained in 56% yield after purification by silica gel column chromatography. Compound **3a** was also obtained in 56% yield by the reaction of **4a** and methyl 3-morpholinocrotonate (**8**)[6] in refluxing C_6H_6. It was not necessary to add morpholine and AcOH for this reaction. When the reaction of equimolar **1a** and **2** was run in the presence of catalytic amounts of morpholine (or piperidine) and AcOH in refluxing C_6H_6, **4a** was obtained in a good yield. Compound **8** (or **9**) was prepared by the reaction of **2** with equimolar morpholine (or piperidine) in the presence of a catalytic amount of AcOH in refluxing C_6H_6.

Reaction of **1a** and 2 molar eq of **2** in the presence of 1 molar eq of piperidine in EtOH for 3 h at room temperature gave 2,4-dimethoxycarbonyl-5-hydroxy-5-methyl-3-phenylcyclohexanone (**5a**)[7] in 86% yield. When the reaction was carried out in refluxing EtOH, 4-methoxycarbonyl-3-methyl-5-phenyl-2-cyclohexenone (**7a**)[8] was obtained in 63% yield. When the reaction of equimolar **1a** and **2** was run in the presence of piperidine and AcOH (also in equimolar amounts) at room temperature, **4a** was obtained in 80% yield without formation of **5a**. Similar reactions were carried out in the presence of morpholine. Reaction of **1a**, **2** and morpholine for 30 h at room temperature gave **5a** in a low yield of 11% after purification by silica gel column chromatography. When a mixture of

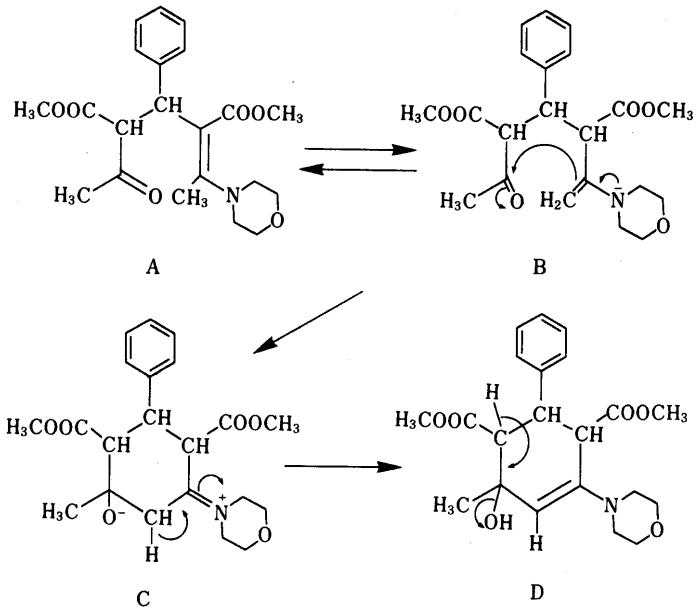


Chart 2

1a, **2** and morpholine was treated in refluxing EtOH, **7a** was obtained in a poor yield of 5%. The reaction of **1a**, **2** and morpholine in the presence of AcOH in EtOH for 30 h at room temperature gave **4a** in 80% yield. It was quite unexpected that the reaction of **1a** and **2** in the presence of morpholine in EtOH had provided **5a** and **7a** in poor yields, compared to the reaction carried out in the presence of piperidine. In a series of reactions in EtOH, piperidine showed a strong catalytic effect, while morpholine significantly slowed the rate of reaction, having a weak catalytic effect compared to piperidine.

The formation of **3a** (or **10a**) from **1a** and **2** in the presence of morpholine (or piperidine) and AcOH, and also by heating **4a** and **8** (or **9**), can be rationalized as shown in Chart 2. Compound **1a** reacts with **2** in the presence of morpholine (or piperidine), which serves as a catalyst, to give **4a**, and the other mole of **2** condenses with morpholine (or piperidine) to give methyl 3-aminocrotonate (**8** or **9**). Michael condensation of **4a** and **8** (or **9**) forms an intermediate A, which is in equilibrium with an intermediate B, and this cyclizes to C and hence to D. Dehydration then leads to **3a**. From the reaction mechanism depicted in Chart 2, **8** (or **9**) can be regarded as an essential intermediate for the preparation of **3a** (or **10a**) under Knoevenagel conditions.

Another route to **3a** was the condensation of **5a** or 4,6-dimethoxycarbonyl-3-methyl-5-phenyl-2-cyclohexenone (**6a**)[9] with morpholine in the presence of titanium tetrachloride ($TiCl_4$) (Chart 3). When **5a** or **6a** was treated with 5 to 6 molar eq of morpholine in the presence of 1 molar eq of $TiCl_4$ in C_6H_6 or $CHCl_3$, **3a** was obtained in a good yield. However, reaction of **6'a**, which is the C-4 epimer of **6a**, with morpholine in the presence of $TiCl_4$ did not produce **3a**. Reaction of **5a** or **6a** with piperidine in the presence of $TiCl_4$ also gave **10a** in a good yield.

Allowing a stoichiometric mixture of $TiCl_4$, secondary amine, and ketone to react leads directly and rapidly to enamine formation.[10] First, $TiCl_4$ reacts with morpholine to give tetrakis(morpholino)titanium (E) as the aminating agent, and then **5a** is dehydrated to **6a** by reaction with the

TABLE II. 6-Aryl-1,5-dimethoxycarbonyl-2-methyl-4-morpholino-1,3-cyclohexadienes (3)

Compd. No.	Reaction time (h)	Yield (%)	mp (°C)	Formula	Analysis (%) Found C	H	N	Cl	Calcd C	H	N	Cl
3a	18	80	114.5—115.5	$C_{21}H_{25}NO_5$	68.87	6.73	3.81		67.91	6.78	3.77	
3b	20	78	148—149	$C_{21}H_{24}N_2O_7$	60.45	5.78	6.70		60.57	5.81	6.73	
3c	8	75	148.5—149.5	$C_{21}H_{24}N_2O_7$	60.48	5.76	6.69		60.57	5.81	6.73	
3d	12	68	186—187	$C_{21}H_{24}N_2O_7$	60.43	5.74	6.68		60.57	5.81	6.73	
3e	20	75	Oil	$C_{22}H_{27}NO_6$								
3f	20	57	162—163	$C_{22}H_{27}NO_6$	65.71	6.69	3.52		65.82	6.78	3.49	
3g	20	51	Oil	$C_{22}H_{27}NO_5$								
3h	20	50	129—130	$C_{22}H_{27}NO_5$	68.43	7.12	3.52		68.55	7.06	3.63	
3i	16	83	101—101.7	$C_{21}H_{24}ClNO_5$	62.31	5.90	3.44	8.90	62.14	5.96	3.45	8.73

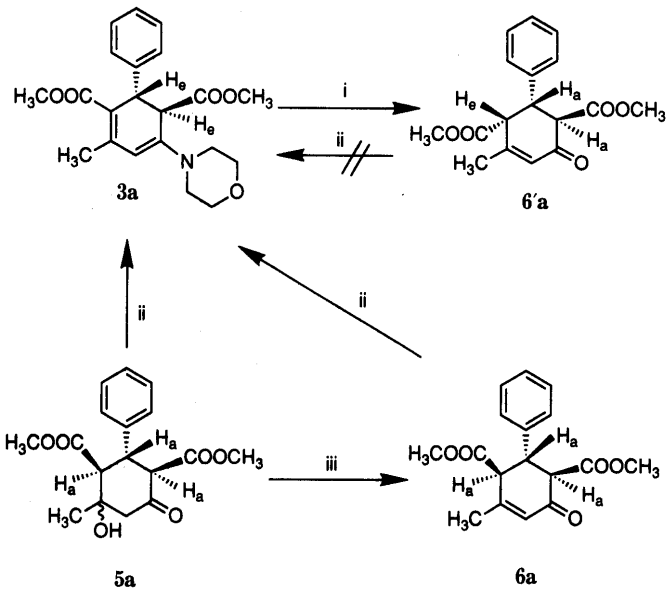


Chart 3

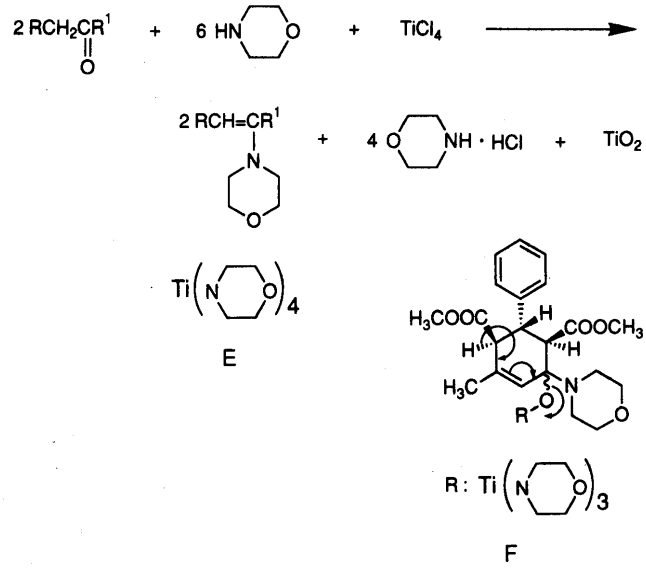


Chart 4

TABLE III. 3-Aryl-2,4-dimethoxycarbonyl-5-hydroxy-5-methyl-1-cyclohexanones (5)

Compd. No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
5a	86	194—195 [lit.[5] 189.5—190.5]	$C_{17}H_{20}O_6$	63.74 (63.54	6.29 6.09)	
5b	80	195—196	$C_{17}H_{19}NO_8$	55.89 (55.85	5.24 5.29	3.83 3.76)
5c	73	191—192	$C_{17}H_{19}NO_8$	55.89 (55.96	5.24 5.30	3.83 3.82)
5d	75	193.5—194.5	$C_{17}H_{19}NO_8$	55.89 (55.78	5.24 5.18	3.83 3.79)
5e	51	165—166	$C_{18}H_{22}O_7$	61.71 (61.67	6.33 6.24)	
5f	47	163—164	$C_{18}H_{22}O_7$	61.71 (61.59	6.33 6.38)	
5g	54	159—159.5	$C_{18}H_{22}O_6$	64.66 (64.78	6.63 6.58)	
5h	49	155.5—156	$C_{18}H_{22}O_6$			
5i	66	187—188	$C_{17}H_{19}ClO_6$	57.55 (57.56	5.40 5.16)	

titanium species. Compound **6a** reacts with the aminating agent E, giving an intermediate F (Chart 4), which is converted into **3a**. In this reaction the titanium atom coordinates with the carbonyl oxygen, preparing the carbonyl group for reaction with the amine base followed eventually by transfer of the oxygen atom to titanium.[10a] $TiCl_4$ is finally converted into titanium(IV) oxide. At present we have no explanation as to why **6'a** did not yield the enamine **3a**.

As shown in Chart 3, **6a** was prepared in 70% yield by dehydration of **5a** by means of an improved procedure in which **5a** was treated with a mixture of polyphosphoric acid (PPA) and AcOH (1 : 1, v/v) in refluxing EtOH. When **3a** was treated with 5% HCl in MeOH at room temperature, **6'a**, the C-4 epimer of **6a**, was obtained in a good yield.

Data for **3**, **5** and **6** prepared here are summarized in Tables II, III and IV. Proton nuclear magnetic resonance (^{1}H-NMR) spectral data of **3**, **5**, **6** and **6'a** are given in Table V.

The stereochemistry of **3a**, **6a** and **6'a** was proposed on the basis of the 360 MHz ^{1}H-NMR coupling constants shown in Table V, compared with the configuration of **5a**

TABLE IV. 5-Aryl-4,6-dimethoxycarbonyl-3-methyl-2-cyclohexenones (6)

Compd. No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
6a	70	130—131 [lit.[5] 134.5—135.2]	$C_{17}H_{18}O_5$	67.54 (67.41	6.00 6.09)	
6b	58	139—140	$C_{17}H_{17}NO_7$	58.79 (58.68	4.93 4.84	4.03 3.87)
6c	64	145—146	$C_{17}H_{17}NO_7$	58.79 (58.63	4.93 5.06	4.03 3.89)
6d	54	123—124	$C_{17}H_{17}NO_7$	58.79 (58.85	4.93 5.09	4.03 3.92)
6e	70	130—131	$C_{18}H_{20}O_6$	65.05 (64.93	6.07 6.13)	
6f	63	124—125	$C_{18}H_{20}O_6$	65.05 (64.97	6.07 6.11)	
6g	75	106—107	$C_{18}H_{20}O_5$	68.34 (68.23	6.37 6.42)	
6h	70	122—123	$C_{18}H_{20}O_5$	68.34 (68.21	6.37 6.41)	
6i	72	131—132	$C_{17}H_{17}ClO_5$	60.63 (60.51	5.09 5.16)	

TABLE V. ^{1}H-NMR Chemical Shifts and Coupling Constants of **3**, **5**, **6** and **6'a**[a]

Compd. No.	Chemical shifts				Coupling constants	
	3-H		6-H	5-H		^5J (5,6)
3a	5.06		4.60 (br s)	3.36 (d)		1.2
3b	5.10		4.70 (br s)	3.32 (d)		1.2
3c	5.10		4.70 (br s)	3.20 (d)		1.6
3d	5.08		4.69	3.30 (d)		0.8
3e	5.05		4.58	3.37 (d)		1.2
3f	5.05		4.54	3.32 (d)		1.1
3g	5.05		4.56	3.35 (d)		1.4
3h	5.05		4.55	3.35 (d)		1.4
3i	5.06		4.58	3.31 (d)		1.6
		4-H	3-H	2-H	^4J (3,4)	^2J (2,3)
5a		3.06 (d)	4.02 (dd)	3.71 (d)	12.0	12.7
5b		3.27 (d)	4.02 (dd)	3.89 (d)	12.3	12.7
5c		3.39 (d)	4.18 (dd)	4.02 (d)	12.0	12.0
5d		3.16 (d)	4.20 (dd)	3.77 (d)	12.3	12.7
5e		3.16 (d)	3.99 (dd)	3.80 (d)	11.9	11.9
5f		3.07 (d)	3.97 (dd)	3.69 (d)	12.0	12.0
5g		3.08 (d)	3.98 (dd)	3.74 (d)	12.3	12.3
5h		3.07 (d)	3.98 (dd)	3.71 (d)	12.3	12.3
5i		3.18 (d)	4.01 (dd)	3.81 (d)	12.3	12.7
	2-H	4-H	5-H	6-H	^4J (4,5)	^6J (5,6)
6a	6.10 (br s)	3.65 (br d)	3.99 (dd)	3.72 (d)	11.0	13.0
6a[b]	5.86	3.28	4.08	3.56	11.2	13.4
6'a	6.10	3.51	3.98	4.57	5.1	13.9
6b	6.14 (br s)	3.7 (br d)	4.154 (dd)	3.74 (d)	11.0	13.0
6c	6.14 (br s)	3.68—3.72 (br d)	4.145 (dd)	3.75 (d)	11.0	13.0
6d	6.13 (br s)	3.67 (br d)	4.14 (dd)	3.72 (d)	11.2	13.3
6e	6.10 (br s)	3.63 (br d)	3.97 (dd)	3.70 (d)	10.7	13.1
6f	6.09 (br s)	3.61 (br d)	3.93 (dd)	3.66 (d)	11.0	13.0
6g	6.09 (br s)	3.64 (dd)	3.95 (dd)	3.70 (d)	10.9	13.0
6h	6.09 (br s)	3.58—3.65 (m)	3.95 (dd)	3.69 (d)	10.9	13.0
6i	6.10 (br s)	3.62 (m)	3.98 (dd)	3.67 (d)	11.0	13.0

a) All the spectra were measured at 360 MHz in $CDCl_3$. b) Reference 5.

which has been reported in the literature.[9] Concerning **3a**, the value of the observed ^5J(5,6) vicinal coupling constant of 1.2 Hz indicates that both hydrogens on C-5 and C-6 are equatorial, and so the phenyl group on C-6 and the ester group on C-5 are in a trans relationship. The vicinal dihedral angle (θ) formed by H-5-C-5(C-6)-H-6 was calculated as about 65° from the coupling constant of 1.2 Hz by using the Karplus equation.[11] The trans relationship of methoxycarbonyl and phenyl groups at C-5 and C-6 of **3a** was the same as that of trans diaxial protons at C-2 and C-3 of **5a**. ^{1}H-NMR data of **6a** and **6'a** shown in Table V indicate that those two ketone derivatives are stereoisomers. Compound **6a** was shown by ^{1}H-NMR spectral examination to have the same stereochemistry at relevant centers as **5a**. Thus, the larger coupling constants 11.0 Hz for ^4J(4,5) and 13.0 Hz for ^6J(5,6) are clearly indicative of trans diaxial hydrogens. The large substituents (C_6H_5 and $COOCH_3$) at neighboring carbons then appear to occupy the preferred equatorial positions. For compound **6'a**, the ^{1}H-NMR evidence indicates that the C-4 methoxycarbonyl group is axial. The magnitude of 13.9 Hz for ^6J(5,6) is indicative of *trans* diaxial hydrogens. The smaller magnitude of 5.1 Hz for ^4J(4,5) shows that those hydrogens are *gauche*: the hydrogen on C-4 is therefore pseudo-equatorial.

The above results may be summarized as follows.

1. New condensation products **3** were obtained in high yields by the reaction of **1**, 2 molar eq of **2**, 1.5 molar eq of morpholine and 0.5 molar eq of AcOH in refluxing C_6H_6. When piperidine instead of morpoline was used, the enamine derivative **10a** was likewise obtained. Compound **8** (or **9**) was shown to be an essential intermediate in the formation of **3a** (or **10a**). Compound **3a** (or **10a**) was also prepared by treating **5a** or **6a** with morpholine (or piperidine) in the presence of $TiCl_4$.
2. Compound **5a** was obtained in a good yield by the reaction of **1a** with 2 molar eq of **2** in the presence of 1 molar eq of piperidine in EtOH at room temperature. When the reaction was carried out in refluxing EtOH, **7a** was obtained as a major product. When the reaction of equimolar **1a** and **2** was run in the presence of piperidine and AcOH in equimolar amounts at room temperature, **4a** was obtained without **5a**. In the reaction in EtOH solution, the use of morpholine resulted in decreasing yields of **5a** and **7a**. Compound **4a** was also prepared by the reaction of equimolar **1a** and **2** in the presence of catalytic amounts of piperidine and AcOH in refluxing C_6H_6. Piperidine was shown to be an excellent catalyst for the reactions in EtOH.
3. Some of **3** exhibited calcium channel-blocking activity in preliminary test.

Experimental

Melting points were measured in a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi Model 260-10 infrared spectrophotometer and ^{1}H-NMR spectra were measured on Hitachi R-90 (90 MHz) and Bruker AM 360 (360 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), br s (broad singlet), d (doublet), t (triplet), m (multiplet) or br (broad). All spectra were consistent with the assigned structures. Combustion analyses were performed on a Perkin-Elmer Model 240C elemental analyzer.

Solvents were dried over Molecular Sieves 4A. All of benzaldehydes and methyl acetoacetate employed in this series were commercial products.

Methyl 3-Morpholinocrotonate (8) This compound was prepared as a viscous oil in 88% yield from **2** (5.8 g, 50 mmol) and morpholine (4.4 g, 50 mmol) in the presence of a catalytic amount of AcOH in C_6H_6 (20 ml) according to the literature[6]; bp 141—143 °C/0.6 mmHg. This oil solidified from the liquid state on standing at room temperature; mp 43—46 °C. *Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.23; H, 8.19; N, 7.50. IR (KBr): 1685 (C=O) cm^{-1}.

Methyl 3-Piperidinocrotonate (9) This compound was prepared in 72% yield according to the procedure described in the literature[6]; bp 111—114 °C/0.1 mmHg.

Preparation of 1,5-Dimethoxycarbonyl-2-methyl-4-morpholino-6-phenyl-1,3-cyclohexadiene (3a) Method A: A mixture of **1a** (0.3 ml, 3 mmol), **2** (0.65 ml, 6 mmol), morpholine (0.4 ml, 4.5 mmol) and AcOH (0.086 ml, 1.5 mmol) in C_6H_6 (10 ml) was stirred for 18 h in refluxing C_6H_6, the water produced being removed azeotropically. The reaction mixture was washed with H_2O and $NaHCO_3$ aqueous solution successively, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with a mixture of C_6H_6 and AcOEt (9:1) to give **3a**, which was recrystallized from a mixture of C_6H_6 and hexane to give analytically pure **3a**.

Other compounds **3** prepared by a procedure similar to that used for **3a** are listed in Table II (elemental analysis) and Table IV (^{1}H-NMR spectral data).

Method B: A mixture of **4a** (6.5 g, 32 mmol) and **8** (5.8 g, 32 mmol) in C_6H_6 (20 ml) was stirred for 8 h in refluxing C_6H_6, the water produced being removed azeotropically. The resulting mixture was taken up in AcOEt (30 ml) and the solution was washed twice with H_2O, dried over $MgSO_4$ and evaporated *in vacuo* to give crystals, which were recrystallized from a mixture of C_6H_6 and hexane to give pure **3a**. Yield: 6.7 g (56%); mp 114—115°C.

Method C: From **5a**: $TiCl_4$ (0.33 g, 1.8 mmol) in dry C_6H_6 (5 ml) was added slowly to a mixture of **5a** (0.50 g, 1.6 mmol) and morpholine (0.82 ml, 9.6 mmol) in dry C_6H_6 (5 ml) at room temperature. The mixture was stirred for 30 min at room temperature and for additional 30 min in refluxing C_6H_6, then poured into ice-water. The mixture was extracted with C_6H_6. The C_6H_6 layer was washed with H_2O and $NaHCO_3$ aqueous solution successively, and dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of C_6H_6 and AcOEt (9:1), followed by recrystallization of the product from a mixture of C_6H_6 and hexane to give pure **3a**. Yield: 0.36 g (60%); mp 114—115 °C.

Method D: From **6a**: $TiCl_4$ (0.19 g, 1.0 mmol) in dry C_6H_6 (5 ml) was added to a mixture of **6a** (0.31 g, 1.0 mmol) and morpholine (0.45 g, 5.0 mmol) in dry $CHCl_3$ (15 ml) at room temperature. The mixture was stirred for 1 h at ambient temperature and then poured into ice-water. The mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of C_6H_6 and AcOEt (9:1), followed by recrystallization of the product from a mixture of C_6H_6 and hexane to give pure **3a**. Yield: 0.24 g (65%); mp 114—115 °C.

The structure of **3a** prepared by methods B to D was confirmed on the basis of IR and ^{1}H-NMR spectral data and mixed melting point test.

1,5-Dimethoxycarbonyl-2-methyl-6-phenyl-4-piperidino-1,3-cyclohexadiene (10a) Method A: A mixture of **1a** (1 ml, 9.8 mmol), **2** (2.2 ml, 20 mmol), piperidine (1.5 ml, 9.8 mmol) and AcOH (0.28 ml, 4.9 mmol) in C_6H_6 (10 ml) was stirred for 8 h in refluxing C_6H_6, the water produced being removed azeotropically. The reaction mixture was cooled to room temperature, washed with 1% HCl aqueous solution, $NaHCO_3$ aqueous solution and H_2O successively, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with a mixture of C_6H_6 and AcOEt (9:1) as an eluent to give **10a** as crystals, which were recrystallized from a mixture of C_6H_6 and hexane to give analytically pure **10a**. Yield: 2.0 g (56%); mp 93—94 °C IR (KBr): 1740, 1680 cm^{-1}. ^{1}H-NMR (90 MHz $CDCl_3$) δ: 1.49 (6H, m), 2.34 (3H, s), 3.08 (4H, m), 3.37 (1H, br s), 3.57 (3H, s), 3.72 (3H, s), 4.56 (1H, br s), 5.01 (1H, s), 7.23 (5H, s). *Anal.* Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.97. Found: C, 71.30; H, 7.51; N, 4.02.

Method B: From **5a**: $TiCl_4$ (1.1 g, 6 mmol) in dry C_6H_6 (10 ml) was added to a mixture of **5a** (1.7 g, 5.3 mmol) and piperidine (2.7 g, 32 mmol) in dry C_6H_6 (34 ml) at room temperature with stirring. The mixture was stirred for 1 h, then poured into ice-water and extracted with C_6H_6. The C_6H_6 layer was washed with H_2O and $NaHCO_3$ aqueous solution successively, dried over $MgSO_4$ and evaporated *in vacuo* to give crystals, which were recrystallized from a mixture of C_6H_6 and hexane to give pure **10a**. Yield: 1.6 g (82%); mp 93—94 °C.

Method C: From **6a**: $TiCl_4$ (0.57 g, 3.0 mmol) in dry C_6H_6 (15 ml) was added to a mixture of **6a** (0.93 g, 3.0 mmol) and piperidine (1.3 g, 15 mmol) in dry $CHCl_3$ (45 ml) at room temperature. The mixture was stirred for 1 h at ambient temperature and then poured into ice-water. The mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of C_6H_6 and AcOEt (9:1), followed by recrystallization of the product from a mixture of C_6H_6 and hexane to give pure **10a**. Yield: 1.0 g (90%); mp 92—94 °C.

Reaction of 6'a with Morpholine in the Presence of $TiCl_4$ The reaction of **6'a** (0.31 g, 1.0 mmol), morpholine (0.45 g, 5.0 mmol) and $TiCl_4$ (0.19 g, 1.0 mmol) in C_6H_6 was carried out according to the same procedure as used for **6a**. The starting material **6'a** was recovered unchanged in 90% yield.

Preparation of 2,4-Dimethoxycarbonyl-5-hydroxy-5-methyl-3-phenyl-1-cyclohexanone (5a) (A) A mixture of **1a** (0.75 g, 5 mmol), **2** (1.1 mg, 10 mmol) and piperidine (0.5 ml, 5 mmol) in 99% EtOH (20 ml) was stirred for 3 h at room temperature. The crystals that formed were collected by filtration, washed with Et_2O and air-dried to give **5a**, which was recrystallized from MeOH to give analytically pure **5a**. Other compounds **5** prepared by procedure similar to that used for **5a** are listed in Table III (elemental analysis) and Table V (^{1}H-NMR spectral data).

(B) A mixture of **1a** (0.5 g, 4.9 mmol), **2** (0.78 g, 4.9 mmol) and morpholine (0.29 g, 4.9 mmol) in 99% EtOH (5 ml) was stirred for 30 h at room temperature. The precipitate was collected by filtration, washed with Et_2O and recrystallized from MeOH to give analytically pure **5a**. Yield: 0.12 g (11%); mp 194—195 °C.

Preparation of 4,6-Dimethoxycarbonyl-3-methyl-5-phenyl-2-cyclohexenone (6a) Dehydration of **5a**: A mixture of **5a** (0.45 g, 1.4 mmol), PPA (1 ml) and AcOH (1 ml) in 99% EtOH (10 ml) was stirred for 5 h in refluxing EtOH. After removal of the solvent, the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo* to give a semicrystalline material, which was triturated with hexane containing a small amount of C_6H_6 to give **6a** as crystals. Recrystallization of crude **6a** from a mixture of Et_2O and petroleum ether gave analytically pure **6a**. Yield: 0.31 g (74%).

Other compounds **6** prepared by a procedure similar to that described above are listed in Table IV (elemental analysis) and Table V (^{1}H-NMR spectral data).

Preparation of 4,6-Dimethyoxycarbonyl-3-methyl-5-phenyl-2-cyclohexenone (6'a) Acid Hydrolysis of **3a**: **3a** (0.5 g) was treated with 5% HCl aqueous solution (5 ml) in MeOH (5 ml) for 1 h at room temperature. After removal of the solvent, the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give a crystalline material, which was recrystallized from EtOH to afford pure **6'a**. Yield: 0.22 g (66%); mp 135—136 °C. IR (KBr): 1730, 1720, 1670 cm^{-1}. *Anal.* Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.30; H, 5.84. ^{1}H-NMR spectral data of **6'a** are summarized together with those of 3, 5 and 6 in Table V.

Preparation of 4-Methoxycarbonyl-3-methyl-5-phenyl-2-cyclohexenone (7a) (A) A solution of **1a** (1 ml, 10 mmol), **2** (2.1 ml, 20 mmol) and piperidine (1 ml, 10 mmol) in 99% EtOH (20 ml) was refluxed for 8 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with 5% HCl aqueous solution and H_2O successively, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of C_6H_6 and AcOEt (9:1) to give **7a** as crystals, which were recrystallized from isopropyl ether to give analytically pure **7a**. Yield: 1.5 g (63%); mp 90—91 °C. IR (KBr): 1730, 1670 cm^{-1}. ^{1}H-NMR (90 MHz $CDCl_3$) δ: 1.97 (3H, s), 2.64 (1H, dd, J=11.2, 5.2 Hz), 2.73 (1H, dd, J=5.2, 11.2 Hz), 3.58 (1H, m), 3.60 (3H, s), 3.67 (1H, m), 6.06 (1H, m), 9.27 (5H, m). *Anal.* Calcd for $C_{15}H_{16}O_3$: C; 73.75, H; 6.60. Found: C; 73.63, H; 6.71.

(B) A mixture of **1a** (1.5 g, 15 mmol), **2** (1.2 g, 30 mmol) and morpholine (0.44 g, 15 mmol) 99% EtOH (15 ml) was stirred for 15 h in refluxing EtOH. Work-up according to the same procedure as described in method A gave analytically pure **7a** in 5% yield. mp 90—91 °C.

Preparation of Methyl Benzylideneacetoacetate (4a) Procedures described in the literature [3-5] were modified. (A) A mixture of **1a** (1.0 g, 10 mmol), **2** (1.2 g, 10 mmol), piperidine (1 ml, 10 mmol) and AcOH (0.57 ml, 10 mmol) in 99% EtOH (15 ml) was stirred for 1 h at room temperature. After 15 min, the mixture was poured into ice-water and extracted with AcOEt. The AcOEt layer was washed with H_2O, 1 N HCl and H_2O successively, dried over $MgSO_4$ and evaporated *in vacuo* to

give an oil. Yield: 1.7 g (85%); bp 120—123 °C/3 mmHg [lit.[4] bp 140 °C/2 mmHg]. ^{1}H-NMR (90 MHz $CDCl_3$) δ: 2.34 and 2.42 (3H, s, $COOCH_3$), 3.74 and 3.84 (3H, s, $COCH_3$), 7.38 and 7.41 (5H, s, ArH), 7.58 and 7.69 (1H, s, $-HC=$). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 71.10; H, 5.80. **4a** was isolated as a mixture of two geometrical isomers.[4]

(B) Reaction of **1a** (1.0 g, 10 mmol), **2** (1.2 g, 20 mmol), morpholine (1.1 ml, 10 mmol) and AcOH (0.57 ml, 10 mmol) in 99% EtOH (15 ml) gave **4a** in 80% yield after purification by column chromatography on silica gel with a mixture of C_6H_6 and AcOEt (9 : 1) as an eluent.

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